Single and combined anti-COVID-19 drugs among hospitalised patients: abridged secondary publication

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KEY MESSAGES

1. Early initiation (within 2 days of hospital admission) of a 5-day remdesivir regimen was associated with improved clinical outcomes and a reduced risk of in-hospital death among patients with moderate COVID-19 who did not require oxygen therapy upon admission.
2. Initiation of remdesivir prior to or concurrently with dexamethasone was associated with a significantly shorter time to clinical improvement and seroconversion as well as a lower risk of in-hospital death among patients hospitalised with moderate COVID-19.
3. Early administration of interferon-β-1b, either alone or in combination with oral ribavirin, was associated with improved survival and reduced need for mechanical ventilation and intensive care among patients with mild to moderate COVID-19.
4. Cardiovascular disorders were the most common complications among post-discharge patients, followed by nephrological and hepatic, haematological, and respiratory disorders.

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Introduction

In response to the COVID-19 pandemic, various pharmaceutical agents were repurposed for the management of hospitalised patients. These included antivirals such as lopinavir-ritonavir, ribavirin, and remdesivir, as well as immunomodulators such as corticosteroids and interferons. The safety and efficacy of these drugs, which act via different mechanisms, may depend on initiation timing and disease severity, given the progression of infection from viral replication to a host hyperinflammatory response. This study aimed to evaluate the effectiveness and adverse effects of antiviral and immunomodulatory drugs in hospitalised patients with COVID-19 in Hong Kong.

Methods

Data from consecutive patients with confirmed COVID-19 admitted to public hospitals in Hong Kong between 6 December 2020 and 31 January 2021 were retrospectively retrieved and analysed. Between 6 December 2020 and 21 January 2021, all patients with a positive polymerase chain reaction result were admitted to public hospitals regardless of disease severity. Patients were categorised based on treatments received during hospitalisation and the time of drug initiation since symptom onset. Patients were followed up until in-hospital death, discharge, treatment crossover, or censoring, whichever occurred first. Outcomes included a composite of death, invasive mechanical ventilation (IMV), or admission to the intensive care unit (ICU) or high dependency unit, as well as time from hospital admission to discharge. Discharge was based on two consecutive negative tests 24 hours apart and clinical assessment by the attending physician.

To determine remdesivir effectiveness, patients who received early intravenous remdesivir (within the first 2 days of admission) were compared with those who received remdesivir after 2 days of admission or who did not receive remdesivir. To determine the effectiveness of combined remdesivir and dexamethasone, patients who received remdesivir before or on the same day as dexamethasone initiation were compared with those who received remdesivir after dexamethasone initiation or those who did not receive remdesivir. To determine adverse events and complications of COVID-19, patients who received lopinavir-ritonavir, ribavirin, remdesivir, interferon-β-1b, dexamethasone, and/or corticosteroids were compared with those who did

not receive any of these medications.

Disease severity was assessed using the World Health Organization (WHO) Clinical Progression Scale (CPS), ranging from 0 (uninfected) to 10 (death).[1] Study outcomes included time to clinical improvement (defined as an improvement of ≥1 point on the WHO CPS), hospital discharge (WHO CPS score ≤3), recovery without oxygen therapy (WHO CPS score ≤4), viral clearance (first negative polymerase chain reaction result), low viral load (cycle threshold value ≥35), first positive immunoglobulin G (IgG) antibody, composite outcome of in-hospital death or IMV (WHO CPS score ≥7), composite outcome of in-hospital death, IMV, or ICU admission, in-hospital death, acute respiratory distress syndrome, hospital length of stay (LOS), and mean change in WHO CPS score from baseline to day 90. Adverse events and complications included newly diagnosed clinical conditions within 18 months after hospital discharge, all-cause mortality, and any disorders. Patients with a prior diagnosis of a specific outcome were excluded from analyses of that outcome. Incidence (events per 10 000 person-years) was estimated for each outcome among cases, controls, and both.

Results

Among patients with mild to moderate COVID-19, use of interferon-β-1b was associated with an improved composite outcome (odds ratio [OR]=0.55, 95% confidence interval [CI]=0.38-0.80) and a shorter LOS (-8.8 days), compared with non-use. Use of oral ribavirin within 7 days of symptom onset was associated with a lower risk of the composite outcome (OR=0.51, 95% CI=0.29-0.90). Use of lopinavir-ritonavir, corticosteroids, and antibiotics did not demonstrate consistent clinical benefit. Co-administration of interferon-β-1b and ribavirin was associated with an improved composite outcome (OR=0.50, 95% CI=0.32-0.78) and a shorter LOS (-2.35 days), compared with interferon-β-1b monotherapy. The combination of interferon-β-1b with lopinavir-ritonavir, with or without ribavirin, yielded results comparable to interferon-β-1b monotherapy in terms of the composite outcome (Table 1).

Among patients with moderate COVID-19, early remdesivir treatment was associated with significantly lower WHO CPS scores from day 30 onwards, compared with matched controls. Early remdesivir use was associated with a significantly shorter time to clinical improvement (median, 13 vs 14 days; hazard ratio [HR]=1.14, 95% CI=1.01-1.29) and a shorter LOS (-2.56 days), as well as a marginally lower risk of in-hospital death (HR=0.58, 95% CI=0.34-0.99). Early remdesivir treatment was also associated with a significantly greater increase in cycle threshold value on day 7. Remdesivir use was significantly associated with a shorter time to achieving a low viral load (median, 9 vs 10 days; HR=1.51, 95% CI=1.24-1.83) and a positive IgG antibody result (median, 6 vs 7 days; HR=1.50, 95% CI=1.31-1.70), compared with matched controls (Table 2).

Compared with dexamethasone alone, combined use of remdesivir and dexamethasone was associated with a significantly shorter time to clinical improvement (median, 12 vs 13 days; HR=1.23, 95% CI=1.02-1.49), a significantly shorter time to a positive IgG antibody result (median, 5 vs 6 days; HR=1.22, 95% CI=1.02-1.46), lower WHO CPS scores from day 5 onwards, a shorter LOS among survivors by 2.65 days, and lower risks of composite outcomes and in-hospital death (HR=0.59, 95% CI=0.36-0.98) [Table 2]. In addition, more rapid recovery was observed in the subgroup of patients who received remdesivir prior to dexamethasone, compared with those who received remdesivir later or not at all. Faster seroconversion and significantly lower risks of composite outcomes and acute respiratory distress syndrome were also observed among those who received remdesivir prior to or concurrently with dexamethasone, compared with those who received remdesivir after dexamethasone.

During the 18-month follow-up period after hospital discharge, patients who had received any of the medications generally showed higher crude incidences of all-cause mortality and various disorders, compared with those who had not received such treatments. Cardiovascular disorders were most common, followed by nephrological and hepatic, haematological, and respiratory disorders (Table 3).

Discussion

In patients with mild to moderate COVID-19, use of interferon-β-1b was associated with improved survival, reduced need for IMV and ICU admission, and a shorter LOS. Compared with the use of lopinavir-ritonavir alone, the combination of lopinavir-ritonavir, ribavirin, and interferon-β-1b was associated with faster symptom resolution, more rapid viral clearance, and reduced LOS in patients with mild to moderate COVID-19.[2] However, the triple-drug regimen did not demonstrate superiority over interferon-β-1b monotherapy. The absence of clinical benefit from lopinavir-ritonavir was consistent with findings from other major trials, possibly due to the ineffectiveness of an acceptable dosage for treating COVID-19.

In a randomised trial involving over 80% of patients hospitalised with moderate COVID-19 who did not require supplemental oxygen, remdesivir was initiated at a median of 2 days after admission. A 5-day course of remdesivir was associated with improved clinical status on days 11 and 14, compared

TABLE 1. Composite outcome of death, invasive mechanical ventilation, or intensive care unit admission among symptomatic COVID-19 patients.

Outcome	No treatment		Treatment		Adjusted odds ratio (95% confidence interval)	Adjusted P value
	Total	No. (%) of events	Total	No. (%) of events		
Interventions initiated regardless of timing						
Antivirals						
Lopinavir-ritonavir	3087	32 (1.0)	1436	51 (3.6)	1.27 (0.81-1.98)	1.000
Ribavirin	3285	52 (1.6)	1238	31 (2.5)	0.58 (0.36-0.92)	0.009
Immunomodulators						
Corticosteroids	3865	7 (0.2)	658	76 (11.6)	1.74 (1.17-2.58)	<0.001
Dexamethasone	3865	7 (0.2)	573	71 (12.4)	3.49 (2.34-5.20)	<0.001
Hydrocortisone	3865	7 (0.2)	96	15 (15.6)	0.27 (0.11-0.64)	<0.001
Methylprednisolone	3865	7 (0.2)	6	2 (33.3)	3.79 (0.31-46.13)	1.000
Prednisolone	3865	7 (0.2)	37	3 (8.1)	0.88 (0.15-5.27)	1.000
Interferon-β-1b	2568	10 (0.4)	1955	73 (3.7)	0.55 (0.38-0.80)	<0.001
Antibiotics	2946	5 (0.2)	1577	78 (4.9)	2.74 (1.56-4.80)	<0.001
Interventions initiated within 7 days of symptom onset						
Antivirals						
Lopinavir-ritonavir	3087	32 (1.0)	1109	40 (3.6)	1.40 (0.88-2.25)	0.370
Ribavirin	3285	52 (1.6)	884	19 (2.1)	0.51 (0.29-0.90)	0.010
Immunomodulators						
Corticosteroids	3865	7 (0.2)	276	42 (15.2)	1.57 (0.97-2.55)	0.084
Dexamethasone	3865	7 (0.2)	225	37 (16.4)	3.46 (2.10-5.72)	<0.001
Hydrocortisone	3865	7 (0.2)	42	6 (14.3)	0.31 (0.09-0.99)	0.046
Methylprednisolone	3865	7 (0.2)	2	0	-	-
Prednisolone	3865	7 (0.2)	14	1 (7.1)	-	-
Interferon-β-1b	2568	10 (0.4)	1581	60 (3.8)	0.60 (0.41-0.88)	0.002
Antibiotics	2946	5 (0.2)	1128	63 (5.6)	3.10 (1.76-5.43)	<0.001
Interventions initiated >7 days after symptom onset						
Antivirals						
Lopinavir-ritonavir	3087	32 (1.0)	327	11 (3.4)	1.01 (0.52-1.94)	1.000
Ribavirin	3285	52 (1.6)	354	12 (3.4)	0.66 (0.36-1.22)	0.556
Immunomodulators						
Corticosteroids	3865	7 (0.2)	382	34 (8.9)	1.85 (1.20-2.87)	<0.001
Dexamethasone	3865	7 (0.2)	348	34 (9.8)	3.50 (2.26-5.43)	<0.001
Hydrocortisone	3865	7 (0.2)	54	9 (16.7)	0.24 (0.07-0.79)	0.008
Methylprednisolone	3865	7 (0.2)	4	2 (50.0)	5.51 (0.44-69.38)	0.556
Prednisolone	3865	7 (0.2)	23	2 (8.7)	0.91 (0.08-10.47)	1.000
Interferon-β-1b	2568	10 (0.4)	374	13 (3.5)	0.39 (0.16-0.91)	0.018
Antibiotics	2946	5 (0.2)	449	15 (3.3)	1.86 (0.82-4.24)	0.322
Composite outcome						
Interferon-β-1b monotherapy	-	-	161	9 (5.6)	Reference	-
Interferon-β-1b + ribavirin			634	16 (2.5)	0.50 (0.32-0.78)	<0.001
Initiated within 3 days of symptom onset	-	-	127	4 (3.1)	1.36 (0.67-2.76)	0.667
Initiated 3 to 7 days after symptom onset	-	-	362	8 (2.2)	Reference	-
Initiated >7 days after symptom onset	-	-	145	4 (2.8)	0.63 (0.26-1.53)	0.489
Interferon-β-1b + lopinavir-ritonavir			752	35 (4.7)	0.88 (0.61-1.28)	1.000
Initiated within 3 days of symptom onset	-	-	194	11 (5.7)	1.14 (0.67-1.96)	1.000
Initiated 3 to 7 days after symptom onset	-	-	424	18 (4.2)	Reference	-
Initiated >7 days after symptom onset	-	-	134	6 (4.5)	0.73 (0.40-1.33)	0.467
Interferon-β-1b + lopinavir-ritonavir + ribavirin			408	13 (3.2)	1.11 (0.77-1.59)	1.000
Initiated within 3 days of symptom onset	-	-	123	8 (6.5)	4.47 (1.46-13.68)	0.005
Initiated 3 to 7 days after symptom onset	-	-	227	3 (1.3)	Reference	-
Initiated >7 days after symptom onset	-	-	58	2 (3.4)	0.70 (0.15-3.25)	1.000

TABLE 2. Comparison of outcomes between COVID-19 patients who received early remdesivir treatment and those who did not, and between those who received remdesivir and dexamethasone and those who received dexamethasone alone.

Outcome	% of patients	% of patients	Hazard ratio (95% confidence interval)	P value
	Early remdesivir	**Control**		
Clinical improvement (≥1 score on WHO CPS)	96.3	84.0	1.14 (1.01-1.29)	0.038
Hospital discharge (score ≤3)	94.0	81.3	1.06 (0.93-1.20)	0.372
Recovery (score ≤4)	83.6	59.6	1.16 (0.87-1.57)	0.314
Viral clearance (first negative PCR result)	36.1	30.4	1.06 (0.87-1.30)	0.552
Low viral load (Ct value ≥35)	40.6	28.1	1.51 (1.24-1.83)	<0.001
Immunoglobulin G antibody	94.0	80.4	1.50 (1.31-1.70)	<0.001
In-hospital death or invasive mechanical ventilation (score ≥7)	10.7	11.3	0.95 (0.67-1.37)	0.796
In-hospital death or invasive mechanical ventilation (score ≥7) or intensive care unit admission	5.9	6.8	0.92 (0.55-1.53)	0.747
In-hospital death, invasive mechanical ventilation, vasopressors, dialysis, or ECMO (score ≥9)	6.0	6.6	0.87 (0.55-1.38)	0.556
In-hospital death (score=10)	4.3	6.7	0.58 (0.34-0.99)	0.045
	Remdesivir-dexamethasone	**Dexamethasone**		
Clinical improvement (≥1 score on WHO CPS)	92.1	88.1	1.23 (1.02-1.49)	0.032
Hospital discharge (score ≤3)	90.6	87.1	1.18 (0.97-1.43)	0.090
Recovery (score ≤4)	79.2	74.5	0.94 (0.72-1.23)	0.663
Viral clearance (first negative PCR result)	32.7	31.6	1.29 (0.93-1.79)	0.126
Low viral load (Ct value ≥35)	31.3	31.2	1.25 (0.91-1.72)	0.177
Immunoglobulin G antibody	97.1	91.7	1.22 (1.02-1.46)	0.029
In-hospital death or invasive mechanical ventilation (score ≥7)	14.5	18.8	0.67 (0.46-0.96)	0.031
In-hospital death or invasive mechanical ventilation (score ≥7) or intensive care unit admission	11.3	17.4	0.64 (0.43-0.97)	0.034
In-hospital death (score=10)	7.7	11.6	0.59 (0.36-0.98)	0.042
Acute respiratory distress syndrome	10.7	8.2	0.99 (0.59-1.66)	0.965

Abbreviations: Ct=cycle threshold, ECMO=extracorporeal membrane oxygenation, PCR=polymerase chain reaction, WHO CPS=World Health Organization Clinical Progression Scale

with standard care, although the time to clinical improvement did not significantly differ.[3] Our findings suggested that early remdesivir treatment resulted in more rapid clinical improvement (reflected by shorter hospital LOS) and lower mortality risk. Such findings may have important implications in healthcare settings with limited resources.

Similarly, combined use of remdesivir and dexamethasone was found to reduce mortality and need for mechanical ventilation, compared with standard care.[4] Our subgroup analyses indicated that remdesivir administration prior to dexamethasone was associated with better clinical outcomes, compared with delayed or no antiviral use. The effect may be more pronounced when remdesivir is introduced prior to or concurrently with dexamethasone, rather than at a later stage. These findings are consistent with the progression of viral infections, where early antiviral administration may help to inhibit viral replication and potentially prevent a cytokine storm. Anti-inflammatory agents subsequently mitigate the hyperinflammatory response, if it arises.

Higher incidences of all-cause mortality and various disorders in the drug exposure group, compared with the non-exposure group, may be explained by the fact that patients who received antivirals and/or immunomodulators had more severe disease at admission and/or more disease progression during hospitalisation, thus requiring initiation of such treatments. Common complications of COVID-19 include thrombosis, cardiovascular events, and acute kidney or liver injury.[5]

Conclusions

Early administration of interferon-β-1b, either alone or in combination with oral ribavirin, was associated with a reduced risk of death or serious complications

TABLE 3. Crude incidences of all-cause mortality and other disorders among COVID-19 patients after discharge.

Outcome	Estimated crude incidence (95% confidence interval)	Person-years
Overall (n=9511)		
All-cause mortality	32.23 (21.74-46.00)	9309
Neurological disorder	40.64 (28.62-56.02)	9104
Psychiatric disorder	157.62 (132.24-186.45)	8628
Respiratory disorder	320.49 (282.57-362.08)	8050
Cardiovascular disorder	3831.70 (3599.12-4075.37)	2639
Haematological disorder	455.76 (408.73-506.71)	7504
Endocrine disorder	165.95 (139.33-196.18)	8255
Nephrological and hepatic disorder	724.96 (664.93-788.95)	7407
Gastrointestinal disorder	19.44 (11.52-30.72)	9260
Dermatological disorder	56.08 (41.75-73.73)	9095
Lopinavir-ritonavir (n=1795)		
All-cause mortality	40.67 (18.60-77.20)	2213
Neurological disorder	46.38 (22.24-85.29)	2156
Psychiatric disorder	246.88 (182.64-326.38)	1985
Respiratory disorder	368.39 (284.91-468.68)	1792
Cardiovascular disorder	6460.01 (5727.97-7259.69)	437
Haematological disorder	1007.45 (857.39-1176.21)	1588
Endocrine disorder	192.51 (134.83-266.52)	1870
Nephrological and hepatic disorder	1263.28 (1098.57-1445.73)	1670
Gastrointestinal disorder	18.19 (4.96-46.56)	2199
Dermatological disorder	88.60 (53.34-138.36)	2145
Ribavirin (n=2117)		
All-cause mortality	49.08 (24.50-87.81)	2241
Neurological disorder	32.23 (12.96-66.41)	2172
Psychiatric disorder	193.22 (137.40-264.14)	2018
Respiratory disorder	366.63 (283.55-466.44)	1800
Cardiovascular disorder	5013.46 (4374.22-5719.83)	441
Haematological disorder	736.69 (607.13-885.70)	1534
Endocrine disorder	216.28 (155.21-293.41)	1896
Nephrological and hepatic disorder	1199.52 (1034.59-1383.25)	1576
Gastrointestinal disorder	27.00 (9.91-58.76)	2222
Dermatological disorder	54.91 (28.37-95.91)	2186
Remdesivir (n=787)		
All-cause mortality	68.48 (18.66-175.34)	584
Neurological disorder	143.21 (61.83-282.18)	559
Psychiatric disorder	224.29 (111.97-401.32)	490
Respiratory disorder	955.89 (661.98-1335.77)	356
Cardiovascular disorder	1331.49 (535.33-2743.38)	53
Haematological disorder	455.47 (183.12-938.44)	154
Endocrine disorder	389.23 (222.48-632.09)	411
Nephrological and hepatic disorder	1035.94 (703.87-1470.44)	299
Gastrointestinal disorder	17.35 (0.44-96.68)	576
Dermatological disorder	53.14 (10.96-155.31)	565

TABLE 3. (cont'd)

Outcome	Estimated crude incidence (95% confidence interval)	Person-years
Interferon-β-1b (n=3229)		
All-cause mortality	68.97 (43.72-103.49)	3335
Neurological disorder	55.89 (33.12-88.33)	3221
Psychiatric disorder	215.68 (166.10-275.42)	2967
Respiratory disorder	481.89 (400.81-574.55)	2573
Cardiovascular disorder	6203.79 (5581.94-6875.98)	585
Haematological disorder	1111.06 (972.97-1263.26)	2097
Endocrine disorder	269.27 (211.06-338.56)	2711
Nephrological and hepatic disorder	1264.09 (1123.24-1417.71)	2310
Gastrointestinal disorder	33.28 (16.61-59.54)	3306
Dermatological disorder	92.98 (62.73-132.73)	3227
Dexamethasone (n=1358)		
All-cause mortality	93.47 (46.66-167.24)	1177
Neurological disorder	98.20 (49.02-175.70)	1120
Psychiatric disorder	285.47 (189.69-412.58)	981
Respiratory disorder	955.39 (743.35-1209.11)	722
Cardiovascular disorder	5672.22 (4453.92-7120.96)	130
Haematological disorder	261 578.29 (224 050.90-303 593.27)	7
Endocrine disorder	397.71 (273.77-558.53)	830
Nephrological and hepatic disorder	2175.11 (1809.15-2593.37)	570
Gastrointestinal disorder	17.24 (2.09-62.29)	1160
Dermatological disorder	132.84 (74.35-219.11)	1129
Corticosteroids (n=1517)		
All-cause mortality	88.14 (45.54-153.96)	1361
Neurological disorder	84.98 (42.42-152.05)	1294
Psychiatric disorder	273.52 (185.84-388.23)	1133
Respiratory disorder	899.88 (710.17-1124.70)	856
Cardiovascular disorder	6034.19 (4839.60-7434.29)	146
Haematological disorder	19 167.97 (16 552.45-22 079.41)	100
Endocrine disorder	378.42 (266.44-521.60)	978
Nephrological and hepatic disorder	2113.33 (1781.16-2489.47)	677
Gastrointestinal disorder	22.38 (4.62-65.40)	1341
Dermatological disorder	130.11 (75.80-208.32)	1307
Without any antivirals (n=5469)		
All-cause mortality	11.70 (4.29-25.46)	5130
Neurological disorder	29.61 (16.57-48.84)	5066
Psychiatric disorder	108.24 (81.08-141.59)	4896
Respiratory disorder	219.59 (179.60-265.83)	4782
Cardiovascular disorder	3094.61 (2848.68-3356.09)	1887
Haematological disorder	169.95 (135.37-210.68)	4884
Endocrine disorder	107.42 (80.23-140.87)	4841
Nephrological and hepatic disorder	421.97 (364.10-486.42)	4503
Gastrointestinal disorder	9.77 (3.17-22.81)	5116
Dermatological disorder	33.71 (19.64-53.97)	5043

in patients with mild to moderate COVID-19; no such association was observed after combined use of lopinavir and ritonavir. Among patients with moderate COVID-19, initiation of a 5-day course of remdesivir within 2 days of admission was associated with substantial clinical and virological benefits. Among dexamethasone users, early or concurrent initiation of remdesivir was superior to delayed or no remdesivir use. When drug supply and healthcare resources permit, early remdesivir treatment should be offered to hospitalised patients with COVID-19. The combination of remdesivir and dexamethasone as well as the initiation of remdesivir prior to dexamethasone are supported.

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Disclosure

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