Remdesiwir w leczeniu COVID-19

3.02.2022

Materiał analityczny przygotowany na potrzeby dyskusji Ekspertów Panelu Farmakoterapia w dniu 3 lutego 2022 r.

Niniejsze opracowanie analityczne stanowi uzupełnienie materiału dowodowego zawartego w rapid review z dnia 05.10.2021 o publikacje zidentyfikowane w ramach przeglądu baz informacji medycznej (PubMed, Embase, medrxiv) za okres 22.09.2021 – 31.01.2022.

Zgodnie z metodyką aktualizacji zaleceń do przeglądu włączono badania kliniczne z randomizacją:

- PINETREE (Gottlieb 2022)
- Sahran 2021

Badanie PINETREE (Gottlieb 2022)- metodyka

PINETREE (Gottlieb 2022)					
Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients					
Methodology	**Population**		**Intervention**	**Control**	**Limitations**
Randomized, double-blind, placebo-controlled trial USA, UK, Denmark, Spain Duration of the study:18.09.2020 – 08.04.2021	N=584 patients Inclusion criteria: • Age ≥ 12 and had at least one preexisting risk factor for progression to severe Covid-19; ≥ 60 regardless of whether they had other risk factors. • at least one ongoing symptom, with onset of the first symptom within 7 days before randomization • SARS-CoV-2 infection confirmed by a molecular diagnostic assay within 4 days before screening Exclusion criteria: • expected to receive supplemental oxygen or hospital care at the time of screening • previous hospitalization for Covid-19, • previously treatment for Covid-19 (including investigational agents), SARSCoV- 2 vaccine.		Ni=279 Remdesivir i.v. - 200 mg on day 1 and 100 mg on days 2 and 3	Nc=283 Placebo	• This trial excluded patients who had received SARS-CoV-2 vaccines;. • This trial was conducted before the emergence of the B.1.617.2 (delta) variant of SARS-CoV-2 as the dominant circulating strain. • The trial was stopped for administrative reasons, and less than half of the planned enrollment was achieved
	Median age (IQR) – yr		50±15	51±15	
	Male sex (%)		53	51	
	BMI		31.2±6.7	30.8±5.8	
	Coexisting conditions, n (%)	Diabetes mellitus	173 (62.0)	173 (61.1)	
		Obesity	154 (55.2)	156 (55.1)	
		Hypertension	138 (49.5)	130 (45.9)	
		Chronic lung disease	67 (24.0)	68 (24.0)	
		Current cancer	12 (4.3)	18 (6.4)	
		Cardiovascular or cerebrovascular disease	20 (7.2)	24 (8.5)	
		Immune compromise	14 (5.0)	9 (3.2)	
	Median duration of symptoms before first infusion (IQR), d		**5 (3–6)**	**5 (4–6)**	

Badanie PINETREE (Gottlieb 2022)- wyniki

Results					
Outcome		**Intervention**	**Control**	**Statistical significance of differences**	
event	**follow-up period**			**Relative parameter (95%CI)**	**Absolute parameter (95%CI)**
Covid-19–related hospitalization or death from any cause by day 28, n/N (%)	28	2/279 (0.7)	15/283 (5.3)	HR=0.13 (0.03; 0.59) ^RR=0.14 (0.03; 0,59)	NNT=22
Covid-19–related medically attended visit or death from any cause, n/N (%)		4/246 (0.7)	15/252 (5.3)	HR=0.19 (0.07; 0.56) ^RR= 0,20 (0.07; 0.56)	NNT=15
Death from any cause by day 28, n/N (%)		0	0		
Hospitalization for any cause by day 28		5/279 (1.8)	18/283 (6.4)	HR=0.28 (0.10; 0.75) ^RR= 0,29 (0.11; 0.76)	NNT=22
Any adverse event, n/N (%)		118/279 (42.3)	131/283 (46.3)	^RR=0.92(0.77; 1.11)	
Serious adverse event, n/N (%)		5/279 (1.8)	19/283 (6.7)	^RR=0.27(0.10; 0.71)	NNH=21
Adverse event - grade 3 or higher, n/N (%)		29/279 (10.4)	23/283 (8.1)	^RR=1,29(0.77; 2.18)	
Authors' conclusion: Among nonhospitalized patients who were at high risk for Covid-19 progression, a 3-day course of remdesivir had an acceptable safety profile and resulted in an 87% lower risk of hospitalization or death than placebo.					

Badanie PINETREE (Gottlieb 2022)- wyniki analizy w podgrupach

Subgroup	Remdesivir	Placebo	Hazard Ratio (95% CI)
	no./total no. of patients (%)		
Residence in the United States	2/264 (0.8)	12/267 (4.5)	0.17 (0.04–0.76)
Age ≥60 yr	1/83 (1.2)	9/87 (10.3)	0.11 (0.01–0.86)
Male sex	1/148 (0.7)	9/145 (6.2)	0.11 (0.01–0.84)
Diabetes mellitus	2/173 (1.2)	14/173 (8.1)	0.14 (0.03–0.63)
Obesity	1/154 (0.6)	9/156 (5.8)	0.11 (0.01–0.88)
Hypertension	2/138 (1.4)	10/130 (7.7)	0.17 (0.04–0.76)
Ethnic group			
Not Hispanic or Latinx	2/146 (1.4)	8/158 (5.1)	0.26 (0.06–1.22)
Hispanic or Latinx	0/123	6/112 (5.4)	—
Chronic lung disease	0/67	4/68 (5.9)	—
Cardiovascular or cerebrovascular disease	0/20	2/24 (8.3)	—
Current cancer	0/12	2/18 (11.1)	—

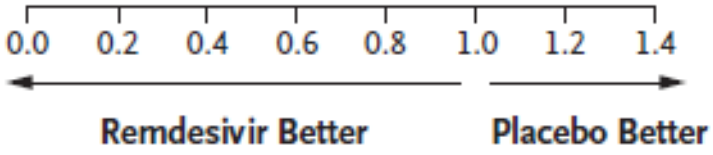

Figure 2. Covid-19–Related Hospitalization or Death from Any Cause at Day 28 in More Than 5% of the Trial Population, According to Demographic and Clinical Characteristics at Baseline.

Badanie Sarhan 2021 - metodyka

Sarhan 2021					
Efficacy of the early treatment with tocilizumab-hydroxychloroquine and tocilizumab-remdesivir in severe COVID-19 Patients					
Methodology	**Population**		**Intervention**	**Control**	**Limitations**
Randomized, cohort study Egypt Duration of the study: 01.10.2020 - 20.03.2021	N=108 Inclusion criteria: • Patients admitted to ICU with confirmed COVID-19 infection through PCR; • after 7 days of isolation with systematic hyperinflammation • radiological findings of CT chest, • increased FiO2to maintain stable O2 saturation or wors-ening O2saturation of >3% with steady FiO2, • elevationon inflammatory marker C-reactive protein (CRP, ≥100 mg/L) orferritin (≥900 ng/mL) and lactate dehydrogenase (LDH, >220 U/L) Exclusion criteria:. • pregnant or lactating women, • hypersensitivity to all drugs or any ingredients of the formulation, • patients with othersevere primary diseases, • serious comorbidities, • history of a psychiatric or neurological disorder, • baseline elevation of ALT AST >3-fold the upper limit		Nc= 52 Tocilizumab + remdesivir tocilizumab 400 mg–800 mg every 24 h for only two doses remdesivir of 200 mg on day 1 followed by 100 mg per day infused over 60 min for 5 days	Ni= 56 Tocilizumab + hydroxychloroquine tocilizumab 400 mg–800 mg every 24 h for only two doses hydroxychloroquine 400 mg twice daily at day1 then 200 mg twice daily for 5 days.	• No specific follow-up period • Small sample size • This trial was conducted before the emergence of the B.1.617.2 (delta) variant of SARS-CoV-2 as the dominant circulating strain.
	Age, yr.		61(52−70)	53(46−68)	
	Gender, male, n (%)		32(61.5%)	45(80.4%)	
	Oxygen saturation%		82(75−88)	85(69−89)	
	Comorbidities, n (%)	Hypertension	29(55.8%)	37(66.1%)	
		Diabetes	25(48.1%)	26(46.4%)	
		Ischemic heart disease	7(13.5%)	16(28.6%)	
		2 or more comorbidities	26(50%)	30(53.6%)	
	Supplemental oxygen at entry,n (%)		**9(17.3%)**	**49(87.5%)**	
	Mechanical ventilation need, n (%)		**43(82.7%)**	**25(44.6%)**	
	ICU admission, n (%)		**50(96.2%)**	**44(78.6%)**	

Badanie Sarhan 2021- wyniki

Results								
Outcome		**Intervention**		**Control**		**Statistical significance of differences**		
event	**follow-up period**					**Relative parameter (95%CI)**	**Absolute parameter (95%CI)**	
Death, n/N (%)	ND	15/52 (28.8%)		12/56 (21.4%)		^RR= 1.346 (0.697; 2.601)		
Length of hospitalization (days)		8 (5−12)		10 (6−16)		p=0.06		
Patient discharge after improvememt, n/N (%)		37/52 (71.2%)		44/56 (78.6%)		p=0.4		
General lab findings		**Baseline**	**Endpoint**	**Baseline**	**Endpoint**			
C-reactive protein level, mg/dl *		125 (43.7−210.8)	20.1 (6.4−40.7)	97 (67.8−139.2)	26 (13.7−79.3)	p=0.07		
D-Dimer level, µg/mL **		0.58 (0.28−1.2)	0.52 (0.32−2.5)	0.48 (0.34−0.88)	0.23 (0.13−0.68)	p<0.001		
PaO2/FiO2 (P/F) ratio ***		113.5 (91.3−176.8)	280 (115−325.3)	120.5 (99.6−218.8)	312 (251.8−465.5)	p=0.25		
Authors' conclusion: Efficacy of both TCZ-RMV and TCZ-HCQ combinations are observed in the treatment of severeCOVID-19 patients; however the increased need for ICU or mechanical ventilation in the TCZ-RMV armcontributed to the appearance of cardiac and thrombotic events.								
* Normal range: 0−8 mg/dl ** Normal range: 0−0.5 µg/mL *** Normal range: >400								