Tocilizumab 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 10.09.2021 r. o publikacje zidentyfikowane w ramach przeglądu baz informacji medycznej (PubMed, Embase, medrxiv) za okres od 27.08.2021 r. do 31.02.2022 r..

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

- **REMDACTA (Rosas 2021)**
- **Naik 2021**
- **Kumar 2021**

Badanie REMDACTA 2021 - metodyka

<table>
<tr><th colspan="5">Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial</th></tr>
<tr><th>Methodology</th><th colspan="2">Population</th><th>Intervention</th><th>Control</th><th>Limitations</th></tr>
<tr><td rowspan="15">Randomized (2:1), double-blind, placebo-controlled, multicenter, phase 3 trial

Europe, North America, South America

Duration of the study: June 2020 – March 2021</td><td colspan="2" rowspan="2">N=649
<u>Inclusion criteria</u>:
• patients aged 12 years and older hospitalized with severe COVID-19 pneumonia
• positive SARS-CoV-2 PCR test result within 7 days of randomization,
• pneumonia confrmed by chest x-ray or computed tomography,
• hypoxemia requiring>6 L/min supplemental oxygen.</td><td>Ni=434;

Tocilizumab + remdesivir
i.v. dose of TOC 8mg/kg (max 800 mg)
(1 or 2 doses)</td><td>Nc=215

Placebo + remdesivir

i.v. dose of placebo</td><td rowspan="15">• The primary outcome was changed to time from randomization to hospital discharge or “ready for discharge” to day 28 (initially: clinical status)

• Inclusion criteria were modified during study to allow enrollment of patients who had received up to 2 doses of remdesivir before randomization.

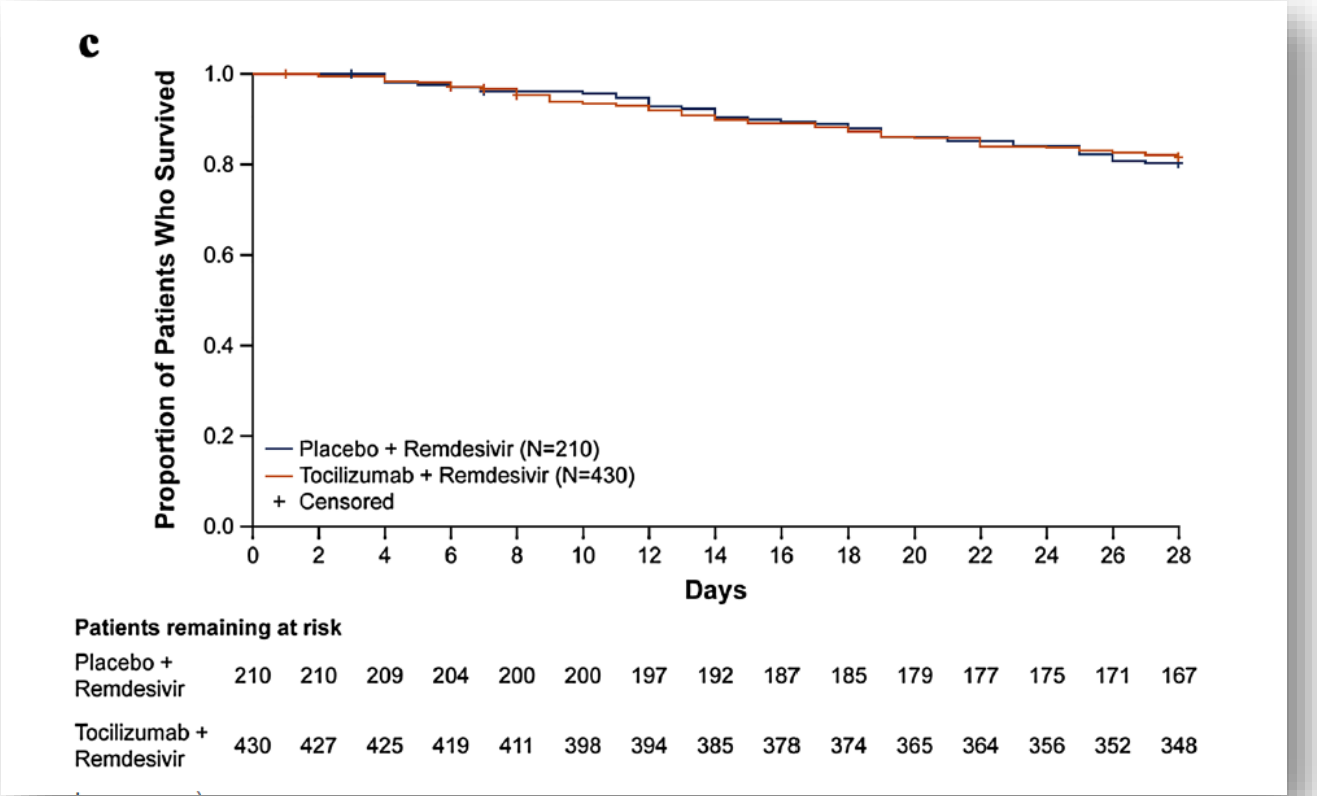
• Approximately three quarters of patients completed the trial to day 28

• Imbalances in baseline characteristics</td></tr>
<tr><td colspan="2">Systemic corticosteroids for treatment of COVID-19 pneumonia were permitted.</td></tr>
<tr><td colspan="2">Age, mean ± SD</td><td>60.1±13.3</td><td>58.2±13.3</td></tr>
<tr><td colspan="2">Male (%)</td><td>61,9</td><td>66,2</td></tr>
<tr><td rowspan="4">Ordinal scale for clinical status (%)***</td><td>3</td><td>6,7</td><td>6,2</td></tr>
<tr><td>4</td><td>78,1</td><td>83,3</td></tr>
<tr><td>5</td><td>9,1</td><td>4,3</td></tr>
<tr><td>6</td><td>6</td><td>6,2</td></tr>
<tr><td colspan="2">Mechanical ventilation (%)</td><td>13,7</td><td>10,5</td></tr>
<tr><td rowspan="2">Corticosteroid use (safety population), n/N (%)</td><td>Baseline</td><td>83,2</td><td>86,4</td></tr>
<tr><td>During the trial to day 28</td><td>88,1</td><td>88,3</td></tr>
<tr><td colspan="2">Remdesivir use before randomization</td><td>83 (19.3)</td><td>40 (19)</td></tr>
<tr><td rowspan="3">Coexisting conditions (%)</td><td>Diabetes</td><td>40</td><td>38.6</td></tr>
<tr><td>Heart disease</td><td>24,4</td><td>21,4</td></tr>
<tr><td>Hypertension</td><td>62,1</td><td>61</td></tr>
<tr><td colspan="2">Time since first COVID-19 symptom, days, mean±SD</td><td>8.8±4.8</td><td>8.9±4.7</td></tr>
</table>

Badanie REMDACTA 2021 - wyniki

Results					
Outcome		Treatment	Control	Statistical significance of differences	
Event	follow-up period			Relative parameter (95%CI) / p value	Absolute parameter
Time to death (days), median	28	NE	NE	HR= 0.95 (0.65; 1.39); p=0,79	-
Mortality, n/N (%)	28	78/430 (18.1)	41/210 (19.5)	p=0,69	Weighted diference= -1.3 [–7.8; 5.2]
	60	97/430 (22.6); [18.6; 26.5]	54/210 (25.7) [19.8–31.6]	p=0,39	Weighted diference= -3 [–10.1; 4]
Patients discharged or "ready for discharge", n (%)	28	284/430 (66)	141/210 (67,1)	RR^=0,98 (0,88; 1,11)	-
Mechanical ventilation or death, n/N (%)		123/430 (28.6)	61/210 (29)	RR^=0,99 (0,76; 1,28)	-
Clinical status at day 14 assessed on the 7-category ordinal scale, mean	14	2.8 (2.6–3)	2.9 (2.6–3.2)	p=0.72	Difference= –0.065 (–0.42; 0.29)
Patients with ≥1 AE, n/N (%)	28	320/430 (74.6)	147/210 (69)	RR^=1,06 (0,96; 1,18)	-
Patients with ≥1 SAE, n/N (%)		128/430 (29.8)	72/210 (33.8)	RR^=0,87 (0,69; 1,10)	-

Badanie REMDACTA 2021 – analiza śmiertelności



Author's conclusion: tocilizumab plus remdesivir did not shorten time to hospital discharge or "ready for discharge" to day 28 compared with placebo plus remdesivir in patients with severe COVID-19 pneumonia, most of whom received systemic corticosteroids. Serious infections were not more frequent with tocilizumab treatment, and no new safety signals were identifed.

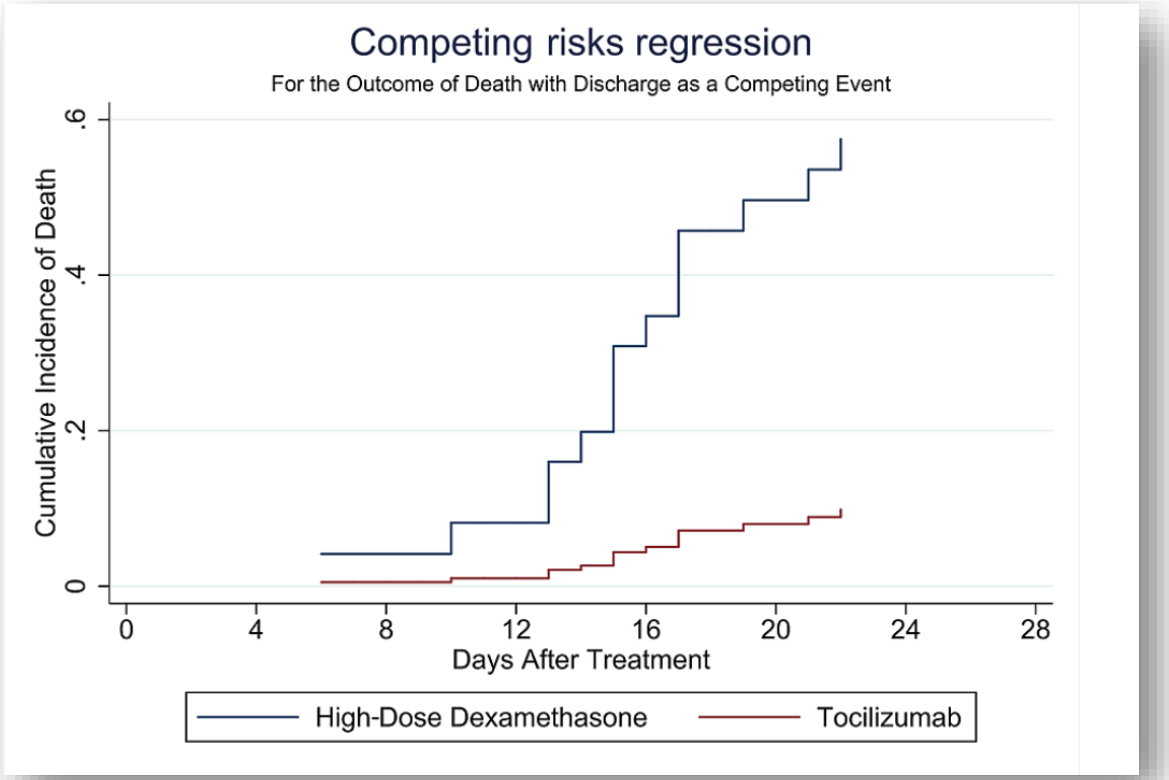
Badanie Naik 2021 - metodyka

High-Dose Dexamethasone Versus Tocilizumab in Moderate to Severe COVID-19 Pneumonia: A Randomized Controlled Trial				
Methodology	**Population**	**Intervention 1**	**Intervention 2**	**Limitations**
Randomized, open-label, trial ITT analysis Duration of the study: May 6 and June 28, 2021 India	**N= 42** <u>Inclusion criteria:</u> • Participants aged 18 years and older; confirmed SARS-CoV-2 infection (RT-PCR); • partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FiO2) ratio of less than 200 on admission; receiving standard care; • clinical worsening in less than 48 hours of the initiation of standard care.	**Nc= 21** **Tocilizumab + Low-dose dexamethasone** single i.v. infusion of TCZ **6 mg/kg** (1 or 2 doses) plus 6 mg dexamethasone for 10 days.	**Ni= 21** **High-dose dexamethasone** i.v. dexamethasone 20 mg once daily for three days plus 6mg dexamethasone by the 10th day .	The trial was discontinued after the first interim analysis, at a limited sample size. The study lacks a control arm. Open-label design. Patients received dexamethasone as standard care in Tocilizumab arm.
		Standard care included: • intravenous (i.v.) remdesivir loading dose of 200 mg on day 1, followed by 100 mg for the next four days; • i.v. dexamethasone 6 mg for 10 days; • therapeutic low-molecular-weight heparin 1.5 mg/kg/day;		
	Median age (IQR) – years	50 (44–65)	51 (45–58)	
	Male sex – n (%)	12 (57.14%)	12 (57.14%)	
	BMI, median (IQR)	27.45 (25.90–30.61)	30.20 (26.4–35.6)	
	Coexisting conditions, n (%) – Diabetes mellitus	8 (38.10%)	7 (33.33%)	
	Coexisting conditions, n (%) – Hypertension	13 (61.90%)	11 (52.38%)	
	Coexisting conditions, n (%) – Asthma	1 (4.76%)	0 (0%)	
	Days from symptom onset on the first dose of intervention, median (IQR), days	8 (7–9)	7 (7–8)	
	Respiratory support at intervention, n (%) – IMV	1 (4.76%)	1 (4.76%)	
	Respiratory support at intervention, n (%) – Noninvasive ventilation	5 (23.81%)	8 (38.10%)	
	Respiratory support at intervention, n (%) – High-flow nasal cannula	15 (71.43%)	12 (57.14%)	
	CRP, median (IQR), mg/dL	111 (74.30–151.40)	89.2 (72–135.70)	
	D-Dimer, median (IQR), ng/mL	649 (389.38–1734.75)	1118 (541.65–3513.1)	

Badanie Naik 2021 - wyniki

Results					
Outcome		Intervention 1	Intervention 2	Statistical significance of differences	
Event	Follow-up			Relative parameter (95%CrI)	Absolute parameter (95%CI)
Primary Outcome: Ventilator-free days, median (IQR)	-	28 (24–28)	0 (0–25)	p= 0.001	-
All-cause mortality, number (%)	28 days	2 (9.52%)	13 (61.90%)	RR^= 0.1538 (0.0395; 0.5996)	NNT=2
Intubation rates posttreatment, n (%)	28 days	2 (9.52%)	13 (61.90%)	RR^= 0.1538 (0.0395; 0.5996)	NNT=2
ICU free, median (IQR), days	28 days	4 (3.5–5.5)	1 (1–5)	p^= 0.017	-
MV duration, median (IQR), days	28 days	0 (0–3)	12 (2.5–15.5)	p^<0.001	-
Discharged from the hospital within 28 days, n (%)	28 days	19 (90.48%)	8 (38.10%)	RR^=2.3750 (1.3531; 4.1687)	NNT=2
SOFA score on treatment day, median, (IQR)	-	5 (4–6)	5 (4–8)	-	-
SOFA score, median, (IQR)	7 days	2 (2–2)	5 (2–7)	p^= 0.002	-
WHO-CPS score on treatment day, median, (IQR)	-	6 (6–6)	6 (6–6)	-	-
WHO-CPS score, median, (IQR)	7 days	5 (3–5)	6 (5–8)	p^<0.001	-
Time to RT-PCR negative status (days), median (IQR)	-	17 (16–17)	19 (17–19)	p^= 0.026	-
Hospital stay, median (IQR), days	-	12 (11–12)	17 (13–17)	p^= 0.003	-

Badanie Naik 2021 – analiza śmiertelności



Author's conclusion: tocilizumab plus remdesivir did not shorten time to hospital discharge or "ready for discharge" to day 28 compared with placebo plus remdesivir in patients with severe COVID-19 pneumonia, most of whom received systemic corticosteroids. Serious infections were not more frequent with tocilizumab treatment, and no new safety signals were identifed.

Badanie Kumar 2021 - metodyka

Kumar 2021				
Safety and Efficacy of Tocilizumab 4 or 8 mg/kg in Hospitalized Patients With Moderate to Severe Coronavirus Disease 2019 Pneumonia: A Randomized Clinical Trial				
Methodology	**Population**	**Intervention I**	**Intervention II**	**Limitations**
Phase 2, open-label, randomized (1:1) study USA	N= 100 <u>Inclusion criteria:</u> • ≥18 years old • hospitalized for moderate to severe COVID-19 pneumonia	N_1= 48 i.v. of tocilizumab 8 mg/kg (1 or 2 doses)	N_2= 49 i.v. of tocilizumab 4 mg/kg (1 or 2 doses)	The study is open-label; The trial was not powered to evaluate efficacy and did not have a placebo arm; Differences in corticosteroid and remdesivir use between groups; Main objective: pharmacokinetic and pharmacodynamic outcomes;
		Standard of care: antiviral treatment, low-dose corticosteroids, supportive care.		
	Male sex, No. (%)	30 (62.5)	27 (55.1)	
	Age, y, mean (SD)	59.8 (14.6)	56.8 (14.3)	
	Disease severity (stratification), No. (%) – Moderate	11 (22.4)	9 (18.8)	
	Disease severity (stratification), No. (%) – **Severe**	**38 (77.6)**	**39 (81.3)**	
	Corticosteroid use, No. (%)	11 (22.4)	11 (22.9)	
	Antiviral treatment, No. (%)	25 (51.0)	19 (39.6)	
	CRP level, Median (range), mg/L	146.6 (5.5–428.2)	157.2 (4.7–438.2)	
	Ferritin level, Median (range), pmol/L	2013.3 (123.6–30 013.2)	1958.3 (51.7–21 768.9)	
	L-6 level, Median (range), ng/L	64.2 (0.0–1820.0)	68.0 (0.0–2540.0)	
	sIL-6R level, Median (range), ng/L	37 900.0 (17 500.0–69 400.0)	35300.0 (18 700.0–60 000.0)	
	Days from first COVID-19 symptom at baseline, median (range)	8.0 (1.0–20.0)	9.0 (3.0–68.0)	

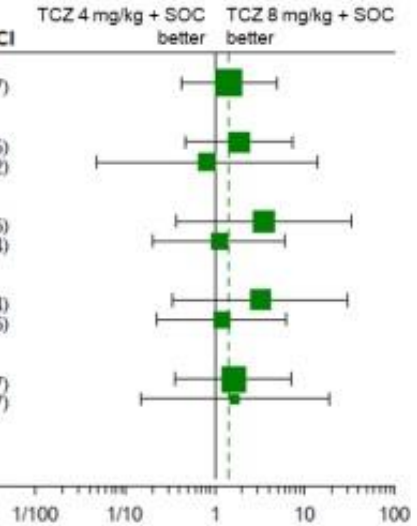
Badanie Kumar 2021 - wyniki

Results					
Outcome		Intervention I	Intervention II	Statistical significance of differences	
Event	Follow-up (days)			Relative parameter (95%CrI)	Absolute parameter
Clinical status based on 7- category ordinal scale, median (95% CI)	14	1.00 (1.00; 3.00)	1.00 (1.00; 3.50)	NA	-
	28	1.00 (1.00; 1.00)	1.00 (1.00; 1.00)	NA	-
Hospital discharge or “ready for discharge” by day 28, n (%)	28	38 (79.2)	39 (79.6)	HR = 0.876 (0.55; 1.40)	-
Mortality rate at day 28, n (%) [95% CI]	28	5 (10.4) [1.8 to 19.1]	7 (14.3) [4.5 to 24.1]	OR= 1.43 (0.42; 4.87)	-
Incidence of mechanical ventilation at day 28, n (%) [95% CI]	28	15 (31.3) [18.1 to 44.4]	14 (28.6) [15.9 to 41.2]	RR^= 1.0938 (0.5943; 2.0129) p^= 0.7734	-
Incidence of initiation of mechanical ventilation at day 28, n (%) [95% CI]	28	8 (19.5) [7.4 to 31.6]	10 (22.2) [10.1 to 34.4]	RR^= 0.8167 (0.3525; 1.8921) p^= 0.6366	-

Badanie Kumar 2021 – analiza wyników w podgrupach

Supplemental Figure 3. Forest Plot of Logistic Regression Analysis of Mortality by Subgroup in Modified Intention-to-Treat Population

Baseline Risk Factors	Total n	TCZ 8mg/kg + SOC (N=48) n	TCZ 8mg/kg + SOC (N=48) Response (%)	TCZ 4mg/kg + SOC (N=49) n	TCZ 4mg/kg + SOC (N=49) Response (%)	Odds Ratio	95% CI
All Patients	97	48	10.4	49	14.3	1.43	(0.42, 4.87)
Sex							
Male	57	30	13.3	27	22.2	1.86	(0.46, 7.45)
Female	40	18	5.6	22	4.5	0.81	(0.05, 13.92)
Age, y							
18 - 65	65	29	3.4	36	11.1	3.50	(0.37, 33.16)
>65	32	19	21.1	13	23.1	1.13	(0.21, 6.14)
Race							
Not-White	59	25	4.0	34	11.8	3.20	(0.34, 30.54)
White	38	23	17.4	15	20.0	1.19	(0.23, 6.26)
Ordinal Clinical Status							
1 to 4	85	41	7.3	44	11.4	1.62	(0.36, 7.27)
5 to 6	12	7	28.6	5	40.0	1.67	(0.15, 18.87)



Author's conclusion: In patients with moderate to severe COVID-19 pneumonia who received tocilizumab 4 or 8 mg/kg, pharmacokinetic and sIL-6R assessments showed expected dose-dependent effects; pharmacodynamic assessments and safety were comparable, with no new safety signals. Further study is required before a lower dose of tocilizumab can be recommended in patients with COVID-19 pneumonia.