Anakinra w leczeniu COVID-19

10.02.2022

Materiał analityczny przygotowany na potrzeby dyskusji Ekspertów Panelu Farmakoterapia w dniu 10 lutego 2022 r.

Niniejsze opracowanie analityczne stanowi uzupełnienie materiału dowodowego zawartego w Rapid Review z dnia 15.09.2021 r. o publikacje zidentyfikowane w ramach przeglądu baz informacji medycznej (PubMed, Embase, medRxiv) za okres od 14.09.2021 r. do 6.02.2022 r.

W ramach przeprowadzonego przeglądu aktualizacyjnego (07.02.2022 r.) zidentyfikowano **2 RCT**:

- **Kharazmi 2021 (*Immunity, inflammation and disease*, 11.11.2021)**;
- **COV-AID – Declercq 2021 (*The Lancet*, 1.12.2021).**

Stanowisko dla anakinry (z dnia 14.09.2021 r.)

Stanowisko Komitetu Sterującego
Nie zaleca się rutynowego stosowania anakinry u pacjentów z COVID-19.

W badaniu REMAP-CAP (pacjenci z ciężkim i krytycznym COVID-19) oraz badaniu CORIMUNO-ANA-1 (pacjenci z łagodnym i umiarkowanym COVID-19) nie wykazano korzystnego efektu stosowania anakinry.

Wyniki próby klinicznej z randomizacją SAVE-MORE (Kyriazopoulou 2021), obejmujące pacjentów z wysokim stężeniem receptora urokinazowego aktywatora plazminogenu (suPAR) w osoczu (≥6 ng/ml), wskazują, że terapia anakinrą u pacjentów z ciężkim zapaleniem płuc w przebiegu COVID-19, wiąże się z ok. 50% redukcją ryzyka zgonu w 28-dniowym okresie obserwacji, w porównaniu do placebo. Stosowanie anakinry może również przynosić korzyści w zakresie skrócenia czasu hospitalizacji i czasu pobytu na OIT, poprawy stanu klinicznego i zapobiegania progresji do niewydolności oddechowej.

Obserwowane korzystne efekty ze stosowania anakinry w populacji z wysokim stężeniem suPAR, są trudne do wykorzystania w praktyce klinicznej w Polsce.

Kharazmi 2021
Metodyka

<table>
<tr><th colspan="5">Kharazmi 2021</th></tr>
<tr><th colspan="5">A randomized controlled clinical trial on efficacy and safety of anakinra in patients with severe COVID-19 (Immunity, inflammation and disease, 11.11.2021)</th></tr>
<tr><th>Methodology</th><th>Population</th><th>Intervention</th><th>Control</th><th>Limitations</th></tr>
<tr>
<td rowspan="2">RCT, open-label, single-center, Phase 3

Randomization: 1:1 (permuted block method)

Stratification: by receiving invasive mechanical ventilation at baseline

Study conduction: May – July 2020

Country: Iran</td>
<td rowspan="2">N=30

<u>Inclusion criteria:</u>
– ≥18 years,
– confirmed diagnosis of COVID-19 based on the RT-PCR test,
– admission to an ICU,
– elevated CRP levels,
– oxygen saturation ≤93%,
– PaO2/FiO2 <300,
– fever or cough or shortness of breath.

<u>Exclusion criteria:</u>
– positive test results for tuberculosis,
– HBV, HCV,
– PLT < 100,000 cells/µl, AST, ALT > 5 ULN,
– untreated active infection,
– previous administration of canakinumab or anakinra.</td>
<td>Ni=15

Anakinra: 100 mg IV, once daily + SoC* for a maximum 14 days or to discharge

(median days for anakinra treatment: 5 (range: 3–9))</td>
<td>Nk=15

SoC*</td>
<td rowspan="2">– small sample size,
– differences in baseline characteristics (age, hypertension, diabetes, coronary artery disease),
– significant difference in baseline respiratory rate (higher in the intervention group),</td>
</tr>
<tr>
<td colspan="2">*The standard protocol recommended dosing and consideration of the related possible effective antiviral and immunomodulatory agents (i.e., remdesivir, lopinavir/ritonavir, interferon, favipiravir, and corticosteroid) and also, oxygen supplementation, ventilation support, fluid, and electrolyte correction, vasoactive agents and antibiotic administration, and renal replacement support if appropriate.</td>
</tr>
</table>

Kharazmi 2021
Charakterystyka pacjentów

Characteristics	Anakinra group ($n = 15$)	Control group ($n = 15$)	p
Age (years)	49.25 ± 19.12	59.00 ± 1.79	.424
Gender			
Male (%)	8	11	.309
Female (%)	7	4	
Body mass index (kg/m^2)	28.20 ± 3.63	27.95 ± 4.93	.874
Vital signs			
Systolic blood pressure (mmHg)	129.87 ± 24.19	120.40 ± 25.82	.309
Diastolic blood pressure (mmHg)	83.87 ± 18.19	74.60 ± 11.99	.174
Pulse rate (beats/min)	96.73 ± 19.28	91.53 ± 10.97	.372
Respiratory rate (breath/min)	26 (3)	22 (5)	.004
O_2 saturation (%)	77.33 ± 13.20	84.07 ± 6.06	.187
CT score	17.42 ± 3.73	16.15 ± 2.70	.340
Hospitalization prior enrollment (days)	4.33 ± 3.67	4.73 ± 3.75	.775
Intubated at baseline	2	2	1.000
Comorbidities			
Hypertension (%)	2 (13.3)	8 (53.3)	.020
Diabetes (%)	3 (20)	8 (53.3)	.058
Coronary artery disease (%)	3 (20)	5 (33.3)	.409

Baseline laboratory data			
WBC (cell/μl)	9200 (4100)	7900 (4830)	.420
Lymphopenia	14	10	.177
Hemoglobin (g/dl)	13.04 ± 2.18	12.01 ± 2.60	.259
INR	1.08 ± 0.10	1.10 ± 0.19	.792
PTT[15]	25.54 ± 4.93	29.80 ± 6.10	.174
Lactate dehydrogenase (U/L)	1149.46 ± 457.52	951.67 ± 408.52	.311
Ferritin (ng/ml)	780.47 ± 311.92	599.50 ± 365.39	.164
C-reactive protein	123.69 ± 49.01	105.10 ± 51.01	.326
Erythrocyte sedimentation rate[15]	48.58 ± 23.38	68.00 ± 24.50	.065
Serum creatinine (g/dL)	1.13 ± 0.25	1.40 (0.7)	.050
Aspartate aminotransferase (U/L)	50.73 ± 19.24	32.64 ± 11.55	.005
Alanine aminotransferase (U/L)	55.86 ± 35.97	29.10 ± 15.83	.016
Medication to treat COVID-19			
Corticosteroid	11	8	.324
Interferon	14	9	.048
Lopinavir/ritonavir	7	12	.052
Remdesivir	2	4	.505
Favipiravir	9	4	.141

Kharazmi 2021

Wyniki

Results						
Outcomes		Follow-up period (days)	Intervention	Control	Relative parameter (RR)	Absolute parameter NNT/NNH
Primary outcome						
Need for endotracheal intubation due to hypoxemia – n/N (%)		Nd	3/15 (20)	10/15 (66,7)	**^0,30 (0,10; 0,88)**	**2 (1; 7)**
Secondary outcomes						
Length of stay (days)	ICU	Nd	5.43 ± 1.72	16.60 ± 9.04	**p=0.010**	
	Hospital		9.50 ± 4.45	19.00 ± 12.04	**p=0.043**	
Clinical status – 7-points ordinal scale	1. Death – n/N (%)	7	4/15 (26.7)	5/15 (33.3)	^0.80 (0.27; 2.41)	-
	2. Hospitalized, on IMV or ECMO – n/N (%)		1/15 (6.7)	5/15 (33.3)	^0.20 (0.03; 1.51)	-
	3. Hospitalized, on non-invasive ventilation or high-flow oxygen – n/N (%)		1/15 (6.7)	0/15 (0)	^3.0 (0.13; 68.26)	-
	4. Hospitalized, requiring low flow supplemental oxygen – n/N (%)		4/15 (26.7)	4/15 (26.7)	^1.0 (0.31; 3.28)	-
	5. Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise) – n/N (%)		1/15 (6.7)	0/15 (0)	^3.0 (0.13; 68.26)	-
	6. Hospitalized, not requiring supplemental oxygen – no longer required ongoing medical care – n/N (%)		0/15 (0)	0/15 (0)	^1.0 (0.02; 47.38)	-
	7. Not hospitalized – n/N (%)		4/15 (26.7)	1/15 (6.7)	^4.0 (0.50; 31.74)	-
	1. Death – n/N (%)	14	5/15 (33.3)	7/15 (46.7)	^0.71 (0.29; 1.75)	-
	2. Hospitalized, on IMV or ECMO – n/N (%)		0/15 (0)	2/15 (13.3)	^0.20 (0.01; 3.85)	-
	3. Hospitalized, on non-invasive ventilation or high-flow oxygen – n/N (%)		0/15 (0)	1/15 (6.7)	^0.33 (0.01; 7.58)	-
	4. Hospitalized, requiring low flow supplemental oxygen – n/N (%)		0/15 (0)	0/15 (0)	^1.0 (0.02; 47.38)	-
	5. Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise) – n/N (%)		0/15 (0)	0/15 (0)	^1.0 (0.02; 47.38)	-
	6. Hospitalizedd not requiring supplemental oxygen –no longer required ongoing medical care – n/N (%)		0/15 (0)	0/15 (0)	^1.0 (0.02; 47.38)	-
	7. Not hospitalized – n/N (%)		10/15 (66.7)	5/15 (33.3)	^2.0 (0.90; 4.45)	-

Kharazmi 2021

Wnioski autorów

Anakinra as an immunomodulatory agent has been **associated with the reduced need for mechanical ventilation in patients admitted to intensive care units because of severe COVID-19. The medication reduced the hospital length of stay.**
Furthermore, no increased risk of infection was observed. Further randomized placebo-controlled trials with a larger sample size are needed to confirm these findings.

COV-AID – Declercq 2021

Metodyka

<table>
<tr><th colspan="8">COV-AID (Declercq 2021)</th></tr>
<tr><th colspan="8">Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial (The Lancet, 1 Dec 2021)</th></tr>
<tr><th>Methodology</th><th>Population</th><th>Intervention1</th><th>Control 1</th><th>Intervention 2</th><th>Intervention 3</th><th>Control 2</th><th>Limitations</th></tr>
<tr>
<td rowspan="2">RCT, open-label, phase 3

2 steps randomisation:
1) 1:2 to anakira or no IL-1 blockade and simultaneously
2) 1:1:1 siltuximab, tocilizumab, or no IL-6 blockade

Stratification: by medical centre

Duration of the study: 3.04.2020- 6.12.2020

Country: Belgium (16 hospitals)</td>
<td rowspan="2">N= 684 (342 – 1st step randomization)

<u>Inclusion criteria:</u>
– ≥ 18 y.o.,
– recent (6-16 days) proven diagnosis of COVID-19 with symptoms,
– admitted to an ICU or specialized COVID-19 ward,
– presence of hypoxia: P/F Ratio <350 mm Hg on room air or <280 mm Hg on supplemental oxygen,
– signs of cytokine release syndrome defined as ANY of the following:
• serum ferritin >1000 mcg/L and rising since last 24h (>2000 µg/L in patients requiring HFO or MV),
• lymphopenia: <800 lymphocytes/µL and 2 of extra criteria*.

<u>Exclusion criteria:</u>
– mechanical ventilation >24h,
– ECMO at time of screening,
– unlikely to survive beyond 48h,
– neutrophil count <1 500 cells/µL,
– PLT < 50 000/µL,
– patients on high-dose systemic steroids or immunosuppressant or immunomodulatory drugs; or anti-IL1 or anti-IL6 treatment,
– active tuberculosis,
– AST, ALT >5 x ULN.</td>
<td>Ni_1= 112

Anakinra: 100 mg s.c., once daily for 28 days or until discharge</td>
<td>Nc_1= 230

receive no IL-1 blockade</td>
<td>Ni_2 = 113

siltuximab: 11 mg/kg i.v., single dose</td>
<td>Ni_3 = 114

tocilizumab: 8 mg/kg i.v., single dose</td>
<td>Nc_2= 115

receive no IL-6 blockade</td>
<td rowspan="2">– the standard of care for patients with COVID-19 changed during the trial,</td>
</tr>
<tr>
<td colspan="5">SoC: Most patients (42%) randomly assigned before August, 2020, received hydroxychloroquine as per standard of care and most patients (84%) randomly assigned from August, 2020, onwards received dexamethasone as per standard of care.</td>
</tr>
</table>

*Extra criteria: Ferritin >700 mcg/L and rising since last 24h, increased LDH (>300 IU/L) and rising last 24h, D-Dimers >1000 ng/mL and rising since last 24h, CRP >70mg/L and rising since last 24h and absence of bacterial infection, if 3 of the above - no need to document 24h rise.

COV-AID – Declercq 2021

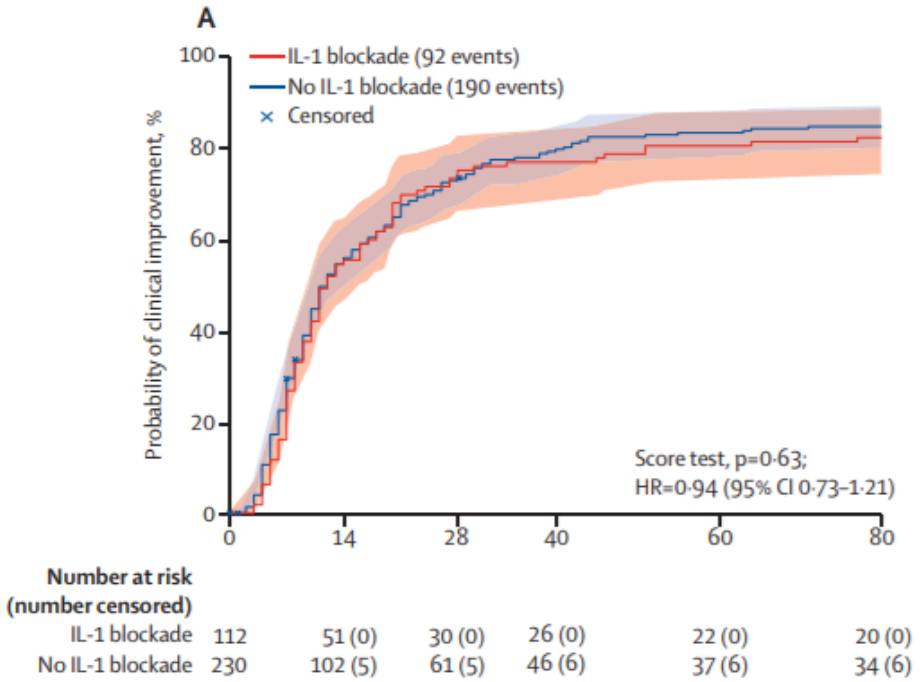
Charakterystyka pacjentów

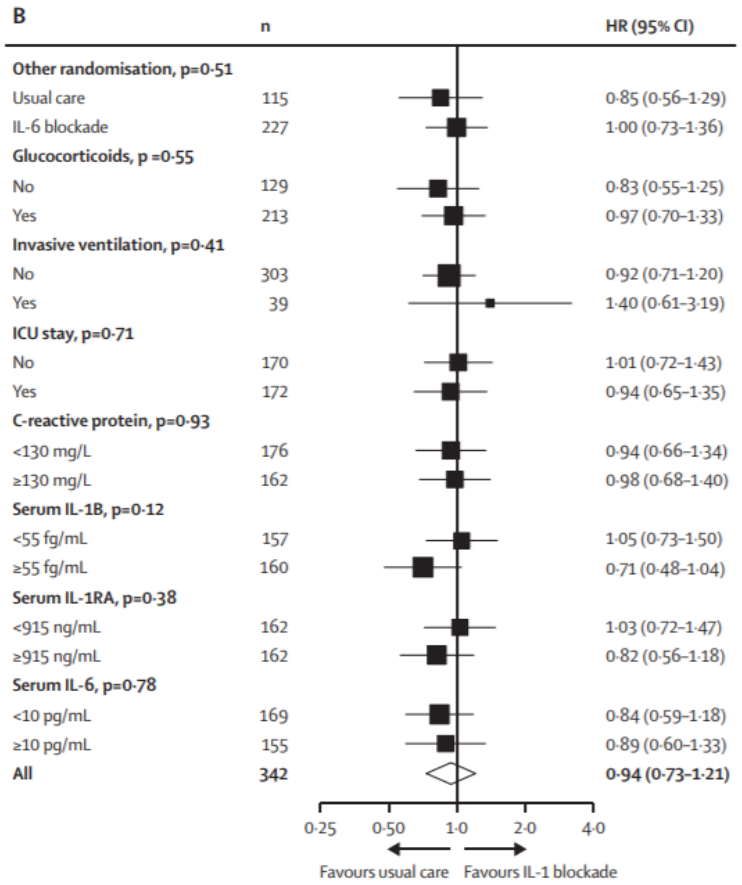
	IL-1 blockade group		No IL-1 blockade group	
	Number of patients	n (%) or median (IQR)	Number of patients	n (%) or median (IQR)
Sex	112	..	230	..
Female	..	25 (22%)	..	52 (23%)
Male	..	87 (78%)	..	178 (77%)
Ethnicity	112	..	230	..
White	..	98 (88%)	..	180 (78%)
Middle Eastern–Arabian	..	11 (10%)	..	29 (13%)
Black	..	1 (1%)	..	8 (3%)
Asian	..	1 (1%)	..	6 (3%)
Other	..	1 (1%)	..	7 (3%)
Age at randomisation, years	112	67 (56–74)	230	64 (54–72)
Body-mass index, kg/m²	108	28 (26–32)	222	28 (26–32)
Smoking	95	..	186	..
No	..	54 (57%)	..	108 (58%)
Current	..	7 (7%)	..	11 (6%)
Former	..	34 (36%)	..	67 (36%)
Co-existing conditions	112	..	230	..
Arterial hypertension	..	57 (51%)	..	104 (45%)
Diabetes	..	37 (33%)	..	58 (25%)
Cardiovascular disease	..	29 (26%)	..	41 (18%)
Chronic kidney disease	..	14 (13%)	..	23 (10%)
6-category ordinal scale at day of randomisation	112	..	230	..
2 hospitalised, on invasive mechanical ventilation	..	17 (15%)	..	22 (10%)
3 hospitalised, on non-invasive ventilation or high flow oxygen devices	..	44 (39%)	..	84 (37%)
4 hospitalised, requiring supplemental oxygen	..	50 (45%)	..	119 (52%)
5 hospitalised, not requiring supplemental oxygen	..	1 (1%)	..	5 (2%)
Days of symptoms at randomisation	100	10 (8–11·5)	214	10 (8–12)
Days of hospitalisation at randomisation	112	3 (2–4)	230	2 (2–4)
Concomitant medication at day of randomisation	112	..	230	..
Antibiotics	..	58 (52%)	..	100 (44%)
Remdesivir	..	6 (5%)	..	11 (5%)
Hydroxychloroquine	..	18 (16%)	..	22 (10%)
Glucocorticoids	..	72 (64%)	..	141 (61%)
Methylprednisolone equivalents per day, mg	72	32 (32–32)	141	32 (32–32)
Duration since randomisation, days	66	8 (5–10)	133	7 (5–9)

COV-AID – Declercq 2021

Wyniki

Results					
Outcomes	**Follow up period (days)**	**Anakinra**	**no IL-1 blockade**	**Relative parameter: HR (95% CI)**	**Absolute parameter**
Primary outcome					
Median time to clinical improvement** – days (95% CI)	28	12 (10; 16)	12 (10; 15)	0,94 (0,73; 1,21)	-
Estimated probability of having experienced clinical improvement at day 28 – % (95% CI)		75 (67; 83)	73 (67; 79)	-	-





**clinical improvement, defined as time from randomisation to an increase of at least two points on a 6-category ordinal scale,

COV-AID – Declercq 2021

Wyniki

Results					
Outcomes	**Follow up period (days)**	**Anakinra**	**no IL-1 blockade**	**Relative parameter HR or expected count ratio (95% CI)**	**Absolute parameter**
Secondary outcomes					
Median time until discharge – days (95% CI)	28	14 (11; 19)	12 (11; 18)	0,90 (0,70; 1,16)	-
Median time until independence from supplemental oxygen or discharge – days (95% CI)		12 (10; 20)	12 (10; 15)	0,91 (0,71; 1,17)	-
Median time until independence from invasive ventilation – days (95% CI)		21 (8; NE)	27 (9; NE)	1,21 (0,54; 2,71)	-
Number of days in hospital – days (95% CI)		19 (17; 22)	19 (17; 21)	1,01 (0,85; 1,21)	-
Number of days in ICU – days (95% CI)		11 (8; 15)	10 (8; 13)	1,05 (0,69; 1,59)	-
Number of days in ICU in patients ventilated at day of randomisation – days (95% CI)		20 (15; 27)	22 (17; 29)	0,89 (0,60, 1,32)	-
Number of days without supplemental oxygen use up to 28 days after randomisation (95% CI)		9 (7; 12)	9 (7; 11)	0,97 (0,68; 1,38)	-
Number days of invasive ventilator (95% CI)		5 (3; 9)	5 (3; 7)	1,05 (0,54; 2,03)	-
Number days of invasive ventilator days in patients ventilated at day of randomisation (95% CI)		15 (11; 20)	16 (13; 21)	0,93 (0,63; 1,37)	-
Number of invasive ventilator-free days (95% CI)		18 (15; 21)	18 (16; 20)	1,00 (0,84, 1,19)	-

COV-AID – Declercq 2021

Wyniki

Safety analysis						
Outcomes		**Follow up period (days)**	**Anakinra (n=44)**	**Anakinra + tocilizumab (n=32)**	**Anakinra + siltuximab (n=36)**	**Usual care (n=74)**
Deaths	n/N (%)	90	10/44 (23)	5/32 (16)	6/36 (17)	9/74 (12)
	^Relative Risk (95% CI)		1.71 (0.74; 3.93)	1.24 (0.45; 3.46)	1.32 (0.50; 3.45)	*Ref.*
Causes of death – n/N (%)	COVID-19		4/44 (9)	2/32 (6)	4/36 (11)	5/74 (7)
	Infectious disorder (not COVID-19)		5/44 (11)	2/32 (6)	2/36 (6)	3/74 (4)
	Nervous system disorder		1/44 (2)	1/32 (3)	-	1/74 (1)
	Other		-	-	-	-
Estimated mortality at day 28 – % (95% CI)		28	16 (8; 13)	13 (5; 30)	17 (8; 33)	10 (5; 20)
Estimated mortality at day 90 – % (95% CI)		90	23 (13; 38)	16 (7; 34)	17 (8; 33)	13 (7; 23)
Serious advent events not leading to mortality – n/N (%)		-	5/44 (11)	5/16 (16)	4/36 (11)	6/74 (8)

COV-AID – Declercq 2021

Wnioski autorów

Drugs targeting IL-1 or IL-6 did not shorten the time to clinical improvement in this sample of patients with COVID-19, hypoxic respiratory failure, low SOFA score, and low baseline mortality risk.

Podsumowanie wyników RCT

Autor badania, rok	Poziom wiarygodności	Ramię badane (N)	Ramię kontrolne (N)	Zgon	Progresja do niewydolności oddechowej	Długość pobytu na OIT	Długość hospitalizacji	Poprawa kliniczna	Całkowite wyzdrowienie	WHO-CPS score	SOFA score	nie-ciężkie AE	SAE
Kharazmi 2021	**E**	15	15		Konieczność intubacji: 20% vs 66,7% ^RR=0,30 (95% CI: 0,10; 0,88)	5,4 vs 16,6 dni p=0,01	9,5 vs 19 dni p=0,04						
COV-AID (Declercq 2021)	B	112	230					czas do poprawy klinicznej					
SAVE-MORE (Kyriazopoulou 2021)	**B**	405	189	3,2 vs 6,9% ^RR=0,47 (95%CI: 0,22; 0,99), NNT=28 HR=0,45 (95%CI: 0,21; 0,98)	HR=0,62 (95%CI: 0,45; 0,87)	10 vs 14 dni HR=2,33 (95%CI: 1,11; 4,92)	11 vs 12 dni HR=1,22 (95%CI: 1,02; 1,47)		*kategoria 1** 50,4 vs 26,5% ^RR=1,90 (95%CI: 1,47; 2,46)	OR=0,36 (95%CI: 0,26; 0,49) *mediana spadku w dniu 14.:* 3 vs 2 OR=0.63 (95%CI: 0.46; 0.85) *w dniu 28:* 4 vs 3 OR=0.40 (95%CI: 0.29; 0.55)	*mediana spadku w dniu 7:* 1 vs 0 OR=0.63 (95%CI: 0.46; 0.86)		
CORIMUNO-ANA-1	**C**	59	55				*wypis ze szpitala*			*mediana punktacji w dniu 14.*			
REMAP-CAP	**C**	365	406										