TRATTAMENTO CON ANTICORPI MONOCLONALI PER L'INFEZIONE DA SARS-COV-2 PAUCISINTOMATICA: ESPERIENZA DELL'OSPEDALE SAN PAOLO DI MILANO

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BACKGROUND – Researches and clinical studies

- 14 mAbs or mAb cocktail were identified and entered in clinical trials. Five of these agents were in Phase 2/3 clinical trials: VIR-7831, LY-CoV555, LY-CoV016, BGB-DXP593, REGN-COV2, and CT-P59
- REGN-COV2: randomized, phase 1-3 trial involving symptomatic non hospitalized patients with COVID-19 (Casirivimab-Imdevimab 2.4 g vs Casirivimab-Imdevimab 8 g vs placebo)
  - This mAB cocktail reduced viral load, with a greater effect in patients whose immune response had not yet initiated or who had a high viral load at baseline
- BLAZE-1 study: randomized, phase 2-3 trial including ambulatory patients who tested positive for SARS-CoV-2 infection and had 1 or more mild to moderate symptoms (Bamlanivimab vs Bamlanivimab-Etesevimab vs placebo);
  - Treatment with Bamlanivimab and Etesevimab, compared with placebo, was associated with a statistically significant reduction in SARS-CoV-2 viral load at day 11; no significant difference in viral load reduction was observed for Bamlanivimab in monotherapy

December 15, 2020: *Tuccori M, Ferraro S, Convertino I, et al.* **Anti-SARS-CoV-2 neutralizing monoclonal antibodies: clinical pipeline**. *MAbs. 2020;12(1):1854149*

January 21, 2021: *Weinreich DM et al.* **REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19.** *NEJM 2021; 384: 238-251; Myron S. Cohen*

January 21, 2021: *Gottlieb RL, Nirula A, Chen P, et al.* **Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial.** *JAMA.2021;325(7):632–644*

BACKGROUND – Therapeutic indications – AIFA (Agenzia Italiana del Farmaco)

- mABs are indicated for the treatment of mild/moderate COVID-19, in adults and adolescents ≥12 years, who do not require supplemental oxygen therapy for COVID-19 and who are high risk of progression to severe COVID-19

- COVID-19 must be confirmed by a positive direct virological test for SARS CoV-2.
- <10 days from symtpoms onset

- *No clinical benefit was observed in patients hospitalized for COVID-19. Therefore, mABs should not be used in patients who:*

  - *are hospitalized for COVID-19*
  - *receive oxygen therapy for COVID-19*
  - *need, due to COVID-19, an increase in the flow of chronic oxygen therapy already in place due to pre-existing co-morbidities.*

February 6, 2021: *Decreto del Ministro della salute n. 32, per il trattamento della malattia da coronavirus 2019 (COVID-19) da lieve a moderata in pazienti adulti e pediatrici,* **Autorizzazione alla temporanea distribuzione dei medicinali a base di anticorpi monoclonali per il trattamento di COVID-19. (21A00788)**

https://www.aifa.gov.it/uso-degli-anticorpi-monoclonali

Inclusion criteria for therapy with monoclonal-ab against SARS-CoV-2

- BMI ≥ 35
- Subjects chronically undergoing peritoneal dialysis or hemodialysis
- Uncontrolled diabetes mellitus (HbA1c ≥ 9.0% 75 mmol / mol) or with chronic complications
- Primery immunodeficiencies
- Secondary immunodeficiencies, with particular regard to onco-haematological patients treated with myelo/immunosuppressive drugs, or less than 6 months after the suspension of treatment
- ≥ 65 years old with at least one additional risk factor
- ≥ 55 years old with:
  - cerebro-vascular disease (including hypertension with concomitant organ damage)
  - COPD and / or other chronic respiratory diseases (people with pulmonary fibrosis or who need O2-therapy for reasons other than SARS-CoV-2
- Age 12– 17 with:
  - BMI 85th percentile for age and gender
  - Sickle cell anemia
  - Congenital or acquired heart disease
  - Diseases of neurodevelopment
  - Dependence on technological devices (e.g. subjects with tracheotomy, gastrostomy, etc.)
  - Asthma, or other chronic respiratory diseases that require daily medications for their control

METHODS

Selection of patients from:

EMERGENCY (SPECIALIST CONSULTANCY)

GENERAL PRACTICE CLINICS

OTHERS (HOSPITALIZED PATIENTS)

Available drugs combinations

- **Bamlanivimab 700mg*** (Eli-Lilly) – infusion time 1 h
- **Bamlanivimab 700mg + Etesevimab 1400 mg** (Eli-Lilly) – infusion time 1 h
- **Casirivimab 1200 mg + Imdevimab 1200 mg** (Regeneron/Roche) – infusion time 30 min

* DETERMINA AIFA del 06/05/2021: stop monotherapy with Bamlanivimab

METHODS – Flow Chart

Procedure	T_0 (infusion)	T_3 (72h)	T_7 (every 7 days till virological clearance)	Follow up
Informed consent	x			
Blood tests	x*		x	x
Nasopharyngeal swab (NS)	x	x	x	
Salivary swab	x	x	x	
Chest Imaging	x°			
Symptoms questionnaire (C19-YRS)	x			x

* if not carried out at least 72 before the evaluation;
° if clinical investigations suspected of initial lung involvement;
‘ 30 days after symptoms resolve

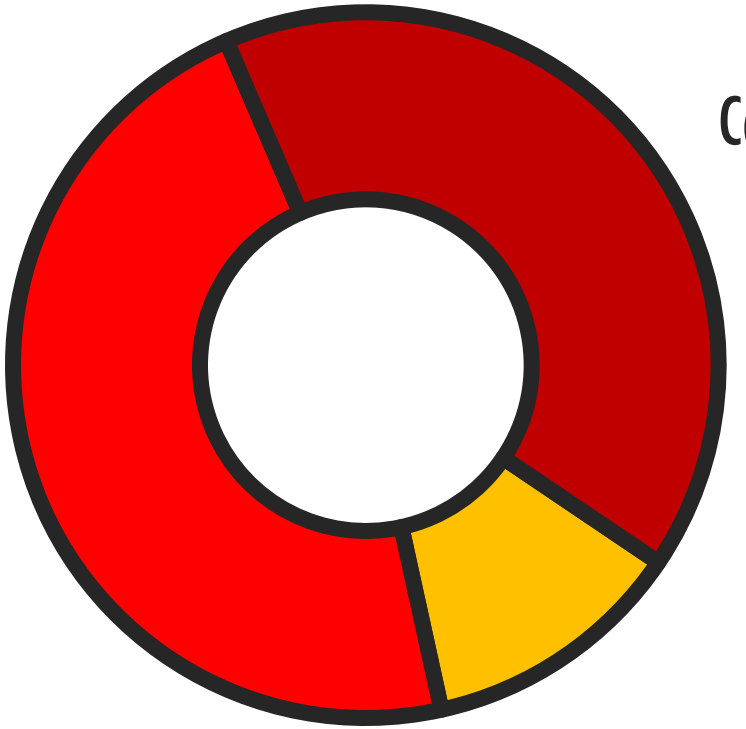
RESULTS - Patients treated (data from 22nd March 2021 to 31st May 2021)

Patients treated

66

Patients with virological recovery	**48** (72,8%)
Patients released from isolation without virological clerance at ≥ 21 days	**12** (22,7%)
Patients still in FU (T_3):	**2** (1,5%)
Patients still in FU (T_7):	**3** (1,5 %)
Patients lost to FU:	**1** (1,5%)

RESULTS – mAbs infused



27
Casirivimab/Imdevimab
(40,9%)

31
Bamlanivimab/Etesevimab
(47%)

8
Bamlanivimab
(12,1%)

RESULTS – Demographic and clinical characteristics

Characteristics	N = 66
Age [years], median (IQR)	63 (51-74)
Male sex, n (%)	33 (50%)
Ethnicity, n (%) Caucasian Hispanic African Asian	 56 (84,8%) 3 (4,5%) 5 (7,6%) 2 (3%)
Risk factor, n (%) BMI>35 Cardio-vascular disease COPD or other respiratory disease Diabetes mellitus Immunodeficiency - HIV/AIDS	 17 (25,7%) 26 (39,6%) 7 (10,6%) 10 (15,2%) 10 (15,2%) 5 (7,6%)
Patients with more than one risk factor, n (%)	9 (13,6%)

RESULTS – Demographic and clinical characteristics

Characteristics	N = 66
Days from symptoms onset, median (IQR)	5 (3-7)
Symptoms onset, n (%)	
1-5 days	37 (56,1%)
6-10 days	29 (43,9%)
Selection of patients, n (%)	
Emergency department	31 (47%)
General medicine clinics/others	25 (38%)
Hospitalized patients	10 (15%)
COVID-19 concomitant therapy, n (%)	
EBPM	49 (74,2%)
Celecoxib	26 (39,4%)
Corticosteroids	15 (22,7%)
Azithromycin	3 (4,5%)
No one (only symptomatic therapy)	14 (21,2%)

RESULTS – FU blood tests

Parameter	T0 (infusion)	T7 (1 week)*	p value
Lymphocytes [10^3 cell/uL], median (IQR)	0,96 (0,58-1,45)	1,57 (1,19-2,16)	<0,001
Platelet count [10^3 cell/uL], median (IQR)	192 (155-223)	294 (234-411)	<0,001
Creatinine [mg/dL], median (IQR)	0,85 (0,7-1,1)	0,80 (0,62-1,00)	0,246
SGOT [U/L], median (IQR)	33 (28-44)	34 (24-44)	0,446
SGPT [U/L], median (IQR)	25,5 (18-39,5)	40 (28-62)	<0,001
CRP [mg/L], median (IQR)	17,2 (6,5-31,9)	9,7 (4,9-22,8)	0,128
D-dimer [ng/mL], median (IQR)	218 (149-381,7)	165 (149-351)	0,936

RESULTS – Outcome (Clinical recovery*)

- Patients with clinical recovery **60** (90,9%)

  17/60 (28,3%) with ongoing symptoms (long COVID)

- Hospitalized patients after infusion **2** (3%)

  1 cPAP, 1 SM (fever and desaturation)

  2/2 (100%) clinically recovered

- Deaths **0**

* At least 72 hours without fever or need for oxygen therapy

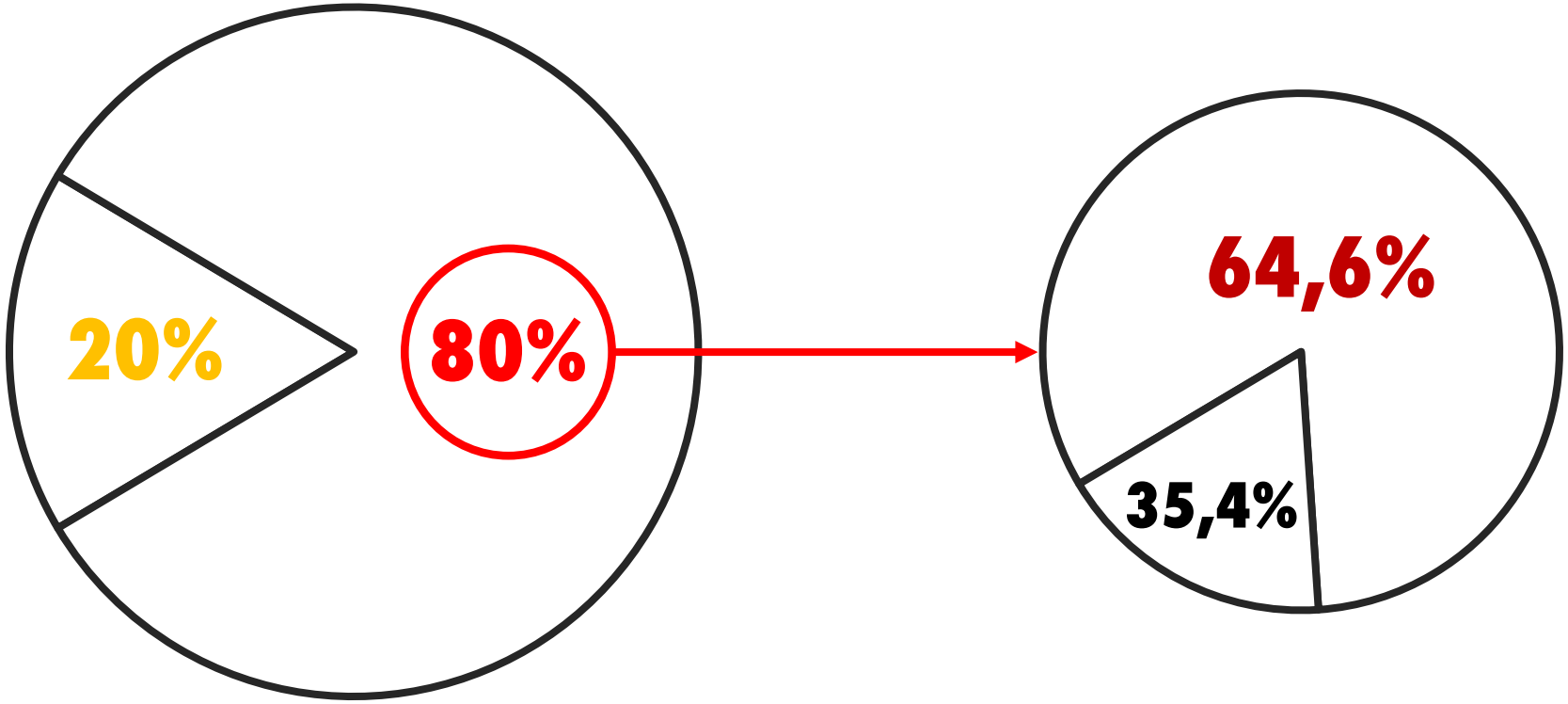
RESULTS – Outcome (Virological recovery*)

Clinical and virological recovery **48/60**

Clinical but no virological recovery **12/60**

Positive at first° nasopharygeal swab **31/48**

Negative at first° nasopharygeal swab **17/48**



* Tested RNA negative to the nasopharyngeal swab

° at T_7

RESULTS – Time at virological recovery

Median time from symptom onsets to **virological** recovery:

- **19 days (15-24)**

Median time from symptom onsets to **clinical** recovery:

- **12 days (10-15)**

RESULTS – Safety

Reported adverse reactions	n 17 (25,7%)
Fever	15 (22,7%)
Nausea/vomit during infusion	1 (1,5%)
Nausea/vomit after infusion	2 (3%)
Neutropenia	1 (1,5%)
Hiccup	1 (1,5%)
Joint inflammation	1 (1,5%)
Hematuria	1 (1,5%)

SAE (Serious Adverse Events) **0**

Mild Adverse Events **17** (25,7%)

Comparison between patients treated at 1-5 days since symptoms onset vs patients treated at 6-10 days

Parameters	1-5 days N 37	6-10 days N 29	p values
Gender, males, n (%)	18 (48,6%)	15 (51,7%)	0,804
Age, median (IQR)	59 (49-71)	70 (55-77)	0,048
Ethnicity, n (%): Caucasian African Hispanic Asian	 30 (81,1%) 5 (13,5%) 1 (2,7%) 1 (2,7%)	 26 (89,7%) 0 2 (6,9%) 1 (3,4%)	0,194
Comorbidities, n (%): BMI >35 Diabetes Cardio-cerebrovascular disease Dialysis COPD Immunodeficiency	 9 (24,3%) 4 (10,8%) 13 (35,1%) 1 (2,7%) 3 (8,1%) 7 (18,9%)	 3 (10,3%) 6 (20,7%) 13 (44,8%) 0 4 (13,8%) 3 (10,3%)	0,386

Comparison between patients treated at 1-5 days since symptoms onset vs patients treated at 6-10 days

Parameter	1-5 days N 37	6-10 days N 29	p values
Lymphocytes [10^3 cell/uL], median (IQR)	1,16 (0,89-1,94)	0,69 (0,51-1,18)	**0,014**
Platelet count [10^3 cell/uL], median (IQR)	179 (147-218)	207 (166-273)	0,089
Creatinine [mg/dL], median (IQR)	0,9 (0,7-1,1)	0,8 (0,75-1)	0,995
SGOT [U/L], median (IQR)	30 (26,5-41)	37 (30-49)	**0,028**
SGPT [U/L], median (IQR)	25 (18-37)	27 (18-42)	0,295
CRP [mg/L], median (IQR)	13 (5,2-19,8)	24,7 (13,3-37,7)	**0,011**
D-dimer [ng/mL], median (IQR)	200 (149-415)	242 (149-367)	0,644

Comparison between patients treated at 1-5 days since symptoms onset vs patients treated at 6-10 days: No difference in efficacy and safety

Parameter	1-5 days N 37	6-10 days N 29	p values
Concomitant treatments for COVID-19, n (%):			
Heparin	29 (80,6%)	20 (69%)	0,281
Corticosteroids	5 (14,3%)	10 (35,7%)	0,047
Days from treatment to virological clearance, median (IQR)	14 (8-20)	14 (9-16)	0,950
First swab, negative; n (%)	10 (27%)	7 (24%)	0,751
Outcome, n (%):			
Clinically and virologically recovered	17 (45,9%)	13 (44,9%)	
Clinically recovered	6 (16,2%)	5 (17,2%)	
Clinically recovered, but long COVID	8 (21,7%)	9 (31,1%)	0,796
Hospitalized	1 (2,7%)	1 (3,4%)	
Ongoing	4 (10,8%)	1 (3,4%)	
Lost to follow up	1 (2,7%)	0	
Adverse events (grade1-2), n (%)	10 (27%)	7 (24,1%)	0,79

Patients treated with combination therapy (bamlanivimab+etesevimab/casirivimab+imdevimab)

Parameters	Combination of mAb, N 58
Gender, males, n (%)	28 (48,3%)
Age, median (IQR)	65 (51-74)
Ethnicity, n (%): Caucasian	 48 (82,8%)
Comorbidities, n (%): BMI >35 Diabetes Cardio-cerebrovascular disease Dialysis COPD Immunodeficiency	 11 (19%) 8 (13,8%) 23 (39,7%) 1 (1,7%) 7 (12,1%) 8 (13,8%)

Patients treated with combination therapy (bamlanivimab+etesevimab/casirivimab+imdevimab)

Parameter	Combination of mAb, N 58
Concomitant treatments for COVID-19, n (%): Heparin Corticosteroids	 41 (71,9%) 13 (23,6%)
Days from treatment to virological clearance, median (IQR)	20 (15-24)
First swab, negative; n (%)	12 (21,8%)
Outcome, n (%): Clinically and virologically recovered Clinically recovered Hospitalized Ongoing Lost to follow up	 40 (69%) 10 (17,2%) 2 (3,4%) 5 (8,7%) 1 (1,7%)
Adverse events (grade1-2), n (%)	16 (27,6%)

LIMITATIONS

- Small **sample size**
- Possible **selection bias** (patients with mild COVID-19 that were unable to come to the hospital or not selected by general practitioners)
- Time to **virological clearance is influenced** by the repetition of swabs to determine virological clearance every 7 days and not every day

CONCLUSIONS

- Monoclonal Abs against SARS CoV-2 showed **high efficacy** >80% in a real-life setting
- These treatments were characterized by **good safety and tolerability** and **easy to use** in outpatient services
- **Efficacy and safety between monotherapy and combination therapy was similar**; for the risk of mutations associated with resistance monotherapy is, however, no more indicated
- We observed a **similar time to virological clearance** between patients who were treated at 1-5 days from symptoms onset and patients who were treated later
- Monoclonal Ab in combinations **seem a promising therapy** for non hospitalized patients with mild COVID-19 and eventually for prevention strategies

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