Remdesivir as a compassionate use in COVID-19 at Lodi hospital, Lombardy

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Abstract

Since 20th of February 2020 COVID-19 epidemic spreaded in Lombardy and our small Hospital had an huge number of cases. We were able to obtain compassionate use of Remdesivir for 19 of them, 12/19 on invasive mechanical ventilation, 7/19 on non-invasive mechanical ventilation. 7/19 (37%) died, 6/19 (32%), the remnant improved (at 28 days since the start of treatment).

Though the interpretation of our results is limited by the size of our sample and the lack of randomized control group, our experience, especially considering the advanced stage of the disease in our patients, seems to suggest that Remdesivir use was useful for our group of patients. Obviously, more conclusive results are expected from ongoing case-control studies as some author recently published.

Summary

We were able to provide Remdesivir on a compassionate-use basis to 19 patients affected by the most severe COVID-19.

We are grateful for the support Gilead give us through the entire period, during which our requests were submitted by means of the dedicated portal.

Of the 19 patients who received Remdesivir, 15 completed the treatment (a tenday course treatment), while 4 patients received at least one dose of the drug.

At baseline, all patients were on mechanical ventilation (ten of them were on invasive support), none was on extracorporeal membrane oxygenation (ECMO).

All the patients were reassessed 28 days after the start of treatment with Remdesivir:

- of the 12 patients on invasive mechanical ventilation 6 were extubated (50%)
- 6 (32%) were discharged
- 7 (37%) died.

At the beginning of the treatment all the7 patients who died were on invasive mechanical ventilation and only one of them completed the entire course of therapy. None of the patients who were not on invasive support died.

We would like share with our little experience and compare it to that one described by Greinet al (1) on NEJM April 10, 2020. Moreover we highlight that even our hospital is a small one, we were able to offer to some of our patients Remdesivir, thanks to the efforts of everyone of the staff and thank to the support of Gilead. We here declare we don't have any conflict of interest in this regard.

From the last decade of February, 2020 Lombardy was very hardly hit by a huge wave of COVID-19, that overwhelmed the Regional Health System, commonly considered one of the most efficient of Italy (2-3).

The health emergency appeared from the beginning as the worst epidemic ever observed by the most expert physicians and statistical data confirmed in a second time that COVID19 has no

comparison in terms of wide spreading and absolute mortality all over the world (4-5) from the time of the Spanish FLU (more than a century ago), with a total death toll over300.000 (6).
ICU and every other wards of Lombard hospitals were almost entirely occupied by COVID-19 patients. Many other ICU and sub-intensive beds were quickly created for facing the need of adequate assistance (8). We needed to treat our patients with oxygen and every other tools of respiratory assistance and mechanical ventilation until to orotracheal intubation and ECMO. On the side of drugs, no treatment had been approved for COVID19 at the time of our experience and no one today except for the recent FDA's emerging authorization of Remdesivir: the emergency use authorization allows for Remdesivir to be distribuited in the US (9-10).
Among the various drugs candidate to be used against COVID-19, their supposed antiviral activity was built essentially on in vitro experience of inihibiting replication of SARS-CoV and SARS-CoV2 in infected vitro cells (11) or anedoctal experience in vivo (12).
Our unresolved distressful dilemma was for several weeks: are we authorized to propose to patients at high risk of dramatic evolution and possibly death, one or more drugs of uncertain effects? On the contrary, is ethically correct to deny a treatment for a patient who invokes it, because of the uncertainty of its effect (amelioration or indifference or worsening)?
In those tragical circumstances we decided to administer various drugs orally and parenterally to every patient who ask for a treatment, after complete information regarding the gap of knowledge about their effects on COVID-19.
On this uncertain basis, we used as supposed antiviral medications hydroxicloroquine, azithromycin, lopinavir/ritonavir, darunavir/cobicistat, alone or in combination, to hundreds of patients admitted to our hospital from the last days of February 2020 (13-14-15-16-17).
We also use Remdesivir, a broad spectrum antiviral nucleotide with potent antiviral activity against a diverse panel of RNA viruses (18), also in mice prophylactic and therapeutic use reduces lung viral loads, improving pulmonary functions (20). Pending randomized placebo controlled trials, the results in a clinical setting can be described as anedoctal, nonetheless we would like to share our human and professional experience.

From 18 March to 24 April Remdesivir was provided by Gilead for compassionate use, which required for Gilead to review all patient clinical information. In particular, the patients had to be hospitalized, SARS- CoV-2 infection confirmed by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) assay and to be in need of oxygen support.
To be eligible for Remdesivir the creatinine clearance had to be above 30 mL/min and the serum ALT ad AST levels had to be less than five times the upper limit of normal range.
The treatment with Remdesivir lasted 10 days and the drug was administered intravenously: the loading dose was 200 mg on day 1, subsequently it was 100 mg a day till the end of therapy on day 10.
Follow-up was conducted at last 28 days after the beginning of the treatment with Remdesivir.
Independent Ethics Committee approval was obtained for each patient and consent was obtain for all patients.
Daily data (from day 1 through day 10) regarding oxygen support requirements, laboratory values and adverse events (if any) where reported.
Follow-up infomation was gathered on 28 day after the beginning of therapy.
We quantified key clinical events on the basis of:

- oxygen support requirement: invasive mechanical ventilation (IMV), non invasive mechanical ventilation requiring (NIMV), Continous Positive Airway Pressure (CPAP), High Flow Nasal Cannulae (HFNC) Oxygen and Low Flow Nasal Cannulae (LFNC) Oxygen, ambient air;
- hospital discharge;
- adverse events (and death) (Table 1).

We adopted the scale (a little modified) introduced in the article "Compassionate Use of Remdesivir for Patients with Severe Covid-19" (1) to assess the improvement of the patients (Table 2):

0) discharged after hospitalization;

1) hospitalized, not requiring supplemental oxygen;
2) hospitalized, requiring supplemental Low-Flow Nasal Cannulae oxygen (LFNC);
3) hospitalized, requiring supplemental High Flow Nasal Cannulae (HFNC) oxygen, but not invasive mechanical ventilation;
4) hospitalized, requiring supplemental not invasive mechanical ventilation (NIMV);
5) hospitalized, requiring supplemental invasive mechanical ventilation (IMV);
6) death.

Table 1. Baseline Demographic and Clinical Characteristics of the Patients

Characteristics	Invasive Ventilation (N=12)	Non invasive Oxygen Support (N=7)	Total (N=19)
Median Age (IQR) - yr	63 (56-68)	65 (57-69)	64 (57-69)
Age Category - no. (%)			
• *< = 65 yr*	7 (53)	4 (57)	11 (58)
• *> 65 yr*	5 (47)	3 (43)	8 (42)
Sex - no. (%)			
• *M*	8 (67)	7 (100)	15 (79)
• *F*	4 (23)	-	4 (21)
Median duration of symptoms before Remdesivir therapy (IQR) - days	21 (16-22)	21 (12-24)	21 (15-22)
Coexisting conditions - no. (%)			
• *Any condition*	7 (58)	3 (43)	10 (53)
• *Hypertension*	6 (50)	2 (29)	8 (42)
• *Ischemic Heart Disease*	3 (25)	-	3 (16)
• *Diabetes*	3 (25)	-	3 (16)

Table 1

			No. Of Patients in Oxygen-Suport Group at Baseline (N)				
			Invasive (N=12)	Non invasive (N=7)	High -flow oxygen (N=0)	Low-flow oxygen (N=0)	Ambient air (N=0)
	Category on ordinal scale	→	6	5	4	3	2
No. (%) Of Patients in Oxygen-Support Group after Treatment (10 days)	Death	6	4 (33)	-	-	-	-
	Invasive	5	5 (42)	-	-	-	-
	Non invasive	4	1 (8)	1 (14)	-	-	-
	High-flow oxygen	3	2 (17)	2 (28)	-	-	-
	Low-flow oxygen	2	-	3 (43)	-	-	-
	Ambient air	1	-	1 (14)	-	-	-
	Discharged	0	-	-	-	-	-
	Improvement		3 (25)	6 (86)	-	-	-
		↑					
	Category on ordinal scale						

			No. Of Patients in Oxygen-Suport Group at 10 days (N)				
			Invasive (N=5)	Non invasive (N=2)	High -flow oxygen (N=4)	Low-flow oxygen (N=3)	Ambient air (N=1)
	Category on ordinal scale	→	6	5	4	3	2
No. (%) Of Patients in Oxygen-Support Group after Treatment (28 days)	Death	6	3 (60)	-	-	-	-
	Invasive	5	-	-	-	-	-
	Non invasive	4	2 (40)	-	-	-	-
	High-flow oxygen	3	-	1 (50)	1 (25)	-	-
	Low-flow oxygen	2	-	-	-	-	-
	Ambient air	1	-	1 (50)	3 (75)	3 (100)	1 (100)
	Discharged	0	-	1 (50)	3 (75)	2 (66)	1 (100)
	Improvement		2 (40)	2 (100)	3 (75)	3 (100)	1 (100)
		↑					
	Category on ordinal scale						

Table 2

Statistical Analysis

Of our 19 patients:

- 15 received the full 10 day course of therapy;
- 2 received 5-9 days of therapy;
- 2 received at least one dose of Remdesivir.

Characteristics of the patients (Table 1):

Men 15, (78.9%), women 4 (21.1%).

Age: range between 48 and 75 yrs (median 64, IQR 57-69).

The median duration of symptoms before Remdesivir therapy was 21 days (IQR 16-22) for patient on mechanical ventilation, compare to 21 days (IQR 12-24) for patients non on mechanical ventilation.

In particular

- 10 showed an improvement regarding the oxygen support (4 patient on invasive support were extubated);
- 6 showed worsening of their clinical conditions (5 died before the completion of the course therapy);
- 2 were stable;
- 7 patient who were on non invasive mechanical ventilation were downgraded in their need for oxygen supplementation).

By the date of the most recent follow-up:

- 12 patients were improved (some discharged on ambient air); the cumulative incidence of clinical improvement was defined by the decrease of 2 points or more on the 6 points scale);
- 7 patients were dead (2 after completing the 10 day course, 5 during the therapy).

All the patients who died were on invasive mechanical ventilation: the median interval between Remdesivir initiation of therapy and death was 7 (IQR 3-9).

None of the patients who were on not invasive mechanical ventilation died during our observation, all of them moreover completed the ten day course of therapy.

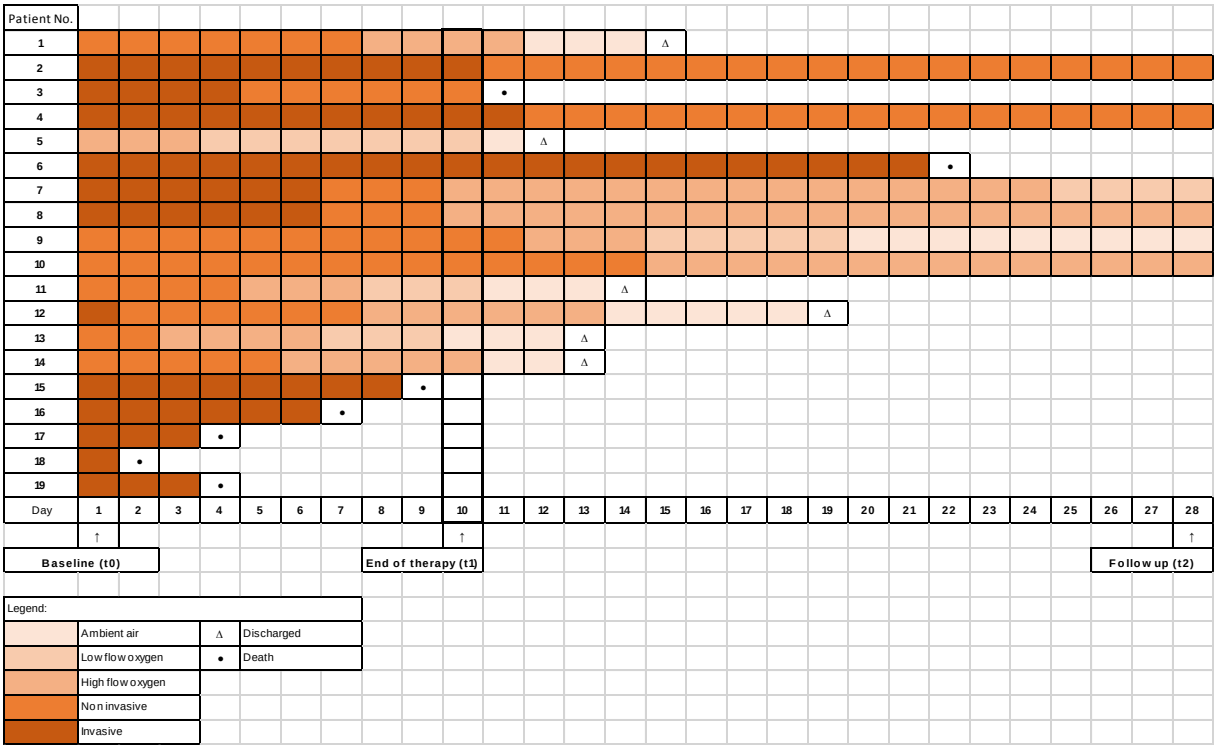

Figure 1

As to safety, figure 1 shows the characteristics of all patients and the adverse events observed while and after the administration of Remdesivir: the most common effect observed was increased hepatic enzymes (even if in a case a patient who had at the beginning of therapy with Remdesivir elevated AST and ALT value – not 5 fold over the upper limit of normal – experienced a decrease of their value in the course of treatment and at the end of ten days the values were within the range).

We did not observe neither rash nor gastrointestinal adverse effects such as diarrhea.

We did observe renal impairment on two patient who were on invasive mechanical ventilation (in one of them this was the reason we had to stop the treatment).

Many of the events observed could be considered as a complication of COVID19 or of the underlying clinical condition (the most common of them was arterial hypertension).

In particular, of the patients who died:

- All of them were on invasive mechanical ventilation;
- 2 died after completion of therapy;
- 5 died before completion of therapy.

Overall mortality from the date of admission was 37%.

Risk of death was greater among patients who were older and among those with coexisting pathological condition.

The analysis population includes all patients who received Remdesivir therapy from 18 March to 24 April and for whom clinical data for at a least 1 subsequent day were available.

We applied descriptive statistics employing indexes as median, IQR and percentages.

Clinical improvement and mortality were described with the Kaplan-Meier survival analysis (used STATA 15) in relation to 2 age group: ≤ 65 years, > 65 years.

Risk of death was greater among patients older than 65 years even if the difference cannot be considered statistically significant (Log Rank Test showed a value of P=0.480) (Figure 2).

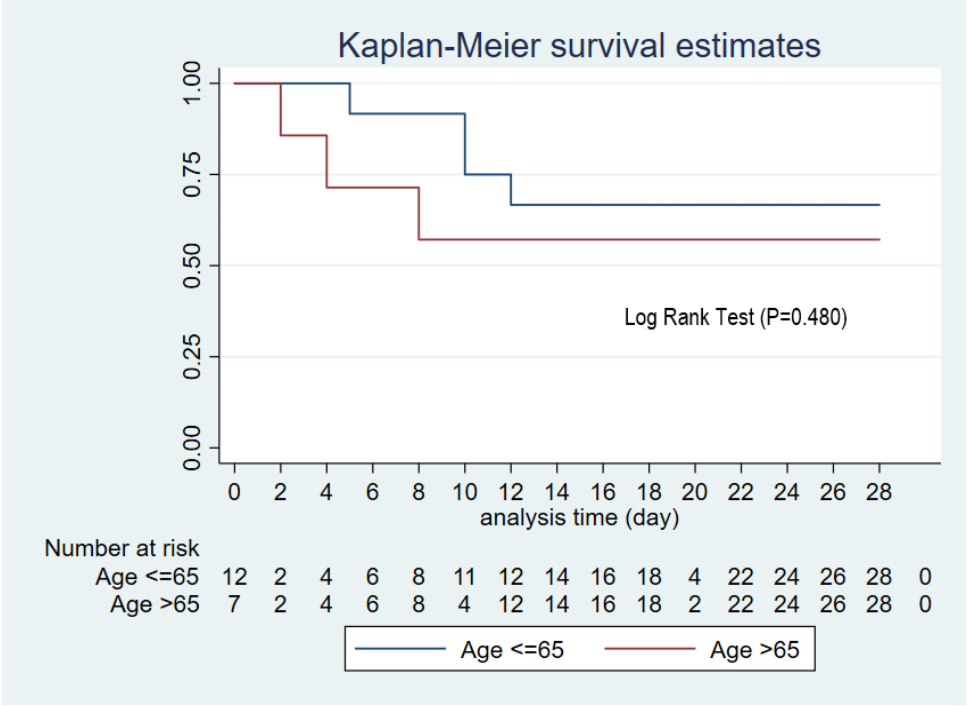

Figure 2

AGE	COMORBIDITY	SERIOUS ADVERSE EVENTS
65	HYPERTENSION	HYPERTENSIVE EPISODE
69	HYPERTENSION; DIABETES	SURGICAL TRACHEOSTOMY
62	SILENT ANAMNESIS	SEPSIS; KIDNEY FAILURE; HYPERTENSION; HEMATOCHEZIA
67	ISCHEMIC HEARTH DISEASE	SURGICAL TRACHEOSTOMY; ATRIAL FIBRILLATION; HYPERTRANSAMINASEMIA; KIDNEY FAILURE; SEPSIS; LYMPHOPENIA; TEMPORAL ATROPHY
62	HYPERTENSION	NOTHING
54	RELATED HBV HEPATOPATHY	HYPERTRANSAMINASEMIA; HYPERTENSION; SURGICAL TRACHEOSTOMY
55	HYPERTENSION; HYPERCHOLESTEROLEMIA; OBESITY	UROSEPSIS; FEMORAL-POPLITEA DVT; PSOAS MUSCLE HEMATOMA;
48	HYPERTENSION; DEPRESSIVE ANXIETY SYNDROME	PULMONARY ABSCESS
51	CHRONIC VENOUS INSUFFICIENCY	HYPERTENSION; EMPYEMA
56	GRANULOMATOSIS WITH POLYANGIITIS	HYPERTRANSAMINASEMIA; LEFT FEMORAL THROMBOSIS IN CENTRAL VENOUS CATHETER
64	SILENT ANAMNESIS	SINUS BRADYCARDIA
56	OBESITY	HYPERTRANSAMINASEMIA; T-WAVE NON-SPECIFIC ANOMALIES
74	SILENT ANAMNESIS	ATRIAL FIBRILLATION
72	DIVERTICULOSIS OF COLON	NOTHING
63	DIABETES MELLITUS; HYPERTENSION; ISCHEMIC HEARTH DISEASE; HEART FAILURE; HEMISPHERICAL ISCHEMIA; DYSLIPIDEMIA	DEATH
67	SILENT ANAMNESIS	DEATH
63	DIABETES MELLITUS: OBESITY; ASTHMA	DEATH
74	ISCHEMIC HEARTH DISEASE; HYPERTENSION; DYSLIPIDEMIA	DEATH
71	HYPERTENSION	DEATH

Table 3

Discussion

In the past ten weeks Lombardy physicians faced one of the most distressful situation of their lives, overwhelmed by an incessant flow of severe cases of COVID-19 to the ER of their hospitals. For the first time in their professional life they experienced the real meaning of inadequate health care resources, in terms of ICU beds, mechanical ventilation equipments, effective drugs. The first two conditions were probably responsible for delayed presentation of COVID-19 severe pneumonia to ICUs and, in many cases, forced the choice of alternative respiratory assistance solutions, instead of invasive mechanical ventilation: data collection and rigorous statistical analysis are needed to understand what were the effects of that situation on the fatality rate of severe COVID-19 in Lombardy in comparison with the ones of other European regions characterized by adequate resources of their health care system. The latter condition forced physicians to propose, in addition

to intensive care assistance, every drug with supposed but not proven efficacy: among them, Remdesivir.

At the present, Remdesivir is under investigation in different randomized clinical trials and expanded access programs in a number of countries as a potential treatment for COVID-19 (9-10). In addition, FDA recently authorized its use "only to treat adults and children with suspected or laboratory confirmed COVID-19 and severe disease defined as SpO2 ≤ 94% on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)", because "it is reasonable to believe that Remdesivir may be effective in treating COVID-19, and that, when used under the conditions described in this authorization, the known and potential benefits of Remdesivir when used to treat COVID-19 outweigh the known and potential risks of such products" (9-10).

More recently, Gilead announced that the Japanese Ministry of Health, Labour and Welfare has approved Remdesivir as a treatment for COVID-19, under an exceptional approval pathway (19).

In our very limited experience, we obtained Remdevisir on a compassionate use basis. Nonetheless, we would like to add our experience to the one published earlier on your journal (1).

The pathway to get the drug was not simple for every patient we considered for the treatment. In the beginning, the drug access was limited to very severe COVD-19 pneumonia (e.g. intubated patients)and as often was the case when the drug was available the clinical conditions were seriously worsened

In particular we observed:

- improvement in oxygen support status in 32 % patients;
- overall mortality 37% over a median follow-up of 28 days as compared to the percentages of the article in question.
- Although it is difficult, if not impossible, to compare our cohort of patients to the one described in the article, it is noteworthy to observe that in both of them most of the patients were severely ill, several were on invasive mechanical ventilation.

In the aforementioned study 34 patients (64%) were on invasive mechanical ventilation.

In our group 10 (53%) were on invasive mechanical ventilation, 9 (47%) were not.

At the end of 10 day course:

- 9 (47%) showed improvement regarding the need for oxygen supplementation, in particular:
- 3 were extubated
- None was discharged
- 5 died.

We observed in conclusion:

- good safelty profile (as shown in Table 3 the adverse events probably related to Remdesivir were relatively little, while the most was attributable to the severity of the illness);
- apparent beneficial effects, with improvement of respiratory function, biochemical profile and general conditions in most of the patients not in invasive mechanical ventilation.

We know that interpretation of our results is limited by the size of our group and the lack of randomized control group. Nevertheless, in general our experience was characterized by the feeling of having a good drug, used mostly in almost desperate clinical situations, whose best utilization could being patients with the first signs of COVID-19 pneumonia.

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Appendix

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Aknowledgements

The authors would like to thank for their precious collaboration all the health personnell involved in tending to these COVID-19 patients, particularly:
Gaia Bombonato MD GP trainee, Teresa Firrito MD GP trainee, Martina Carugi MD GP trainee, Giammarco Russo MD GP trainee, Luca Mugnaga MD ICU, Alban Beltoja MD ICU, Laura Mariconti MD ICU, Adriana Manuela Nailescu MD ICU, Isabella Costa MD ICU, Loredana Pitagora MD ICU, Laura Maderna MD ICU, Annalisa Malara MD ICU, Maria Antonella Matera MD ICU, Maria Antonia Pedrazzini MD ICU, Pier Giorgio Villani MD ICU, Roberto Dossena MD ICU, Leonardo Castellazzi MD ICU, Cristina Quartarone MD ICU, Omar Alquati MD ICU, Maria Antonella Premoli MD ICU, Nicolò Maria Vanoni MD Pneumologist, Sonia Henchi MD Pneumologist, Monica Crepaldi MD Pneumologist, Mariano Scozzafava MD Pneumologist, Alice Claudia Repossi MD Pneumologist, Irene Raimondi Cominesi MD Cardiologist, Marco Cesarano MD Cardiologist, Claudia Vecchiato MD Cardiologist, Paola Alessandra Sepe MD Cardiologist, Michela Fiini MD Cardiologist, Mirko Marra MD GP trainee, Alessandra Brocchieri MD Internal Medicine, Guja Minoja MD Internal Medicine, Simone Marino Pasini MD Internal Medicine, Eva Scorletti MD Internal Medicine, Veronica Pacetti MD Internal Medicine, Luisella Ferrari MD Internal Medicine, Paola Ilaria Bianchi MD Internal Medicine, Francesca Dall'Ara MD Internal Medicine, Monia Vezzoli MD Internal Medicine, Antonella Dedé MD Internal Medicine, Filippo La Marca MD Urologist, Francesco Broglia MD Gastroenterologist, Andrea Rovati MD Internal Medicine, Elena Esposti MD GP trainee, Sabrina Iachetti Chief Nurse of Subintensive Unit, Damiano Pochetti Chief Nurse of ICU, Elena Gambarana Chief Pharmacist, Eleonora Dogliani Pharmacist dr.