Département de médecine
Faculté de médecine
Université de Montréal

COVID-19 persistant chez une patiente sous Rituximab avec clairance virale post tixagevimab-cilgavimab

Présenté par Qi Li – R2 tronc commun de médecine interne

Sous la supervision de Dre Madeleine Durand – interniste, CHUM; Dr Simon Grandjean Lapierre – microbiologiste-infectiologue, CHUM

Avec l'aide de Dre Karima Zerrouki – future R1 tronc commun de médecine interne

Conflits d’intérêts

Aucun

Objectifs pédagogiques

1. Reconnaître le diagnostic différentiel et le jugement clinique.
2. Réviser les modes de présentation clinique et d'investigation de diverses maladies plus rares.

Présentation du cas

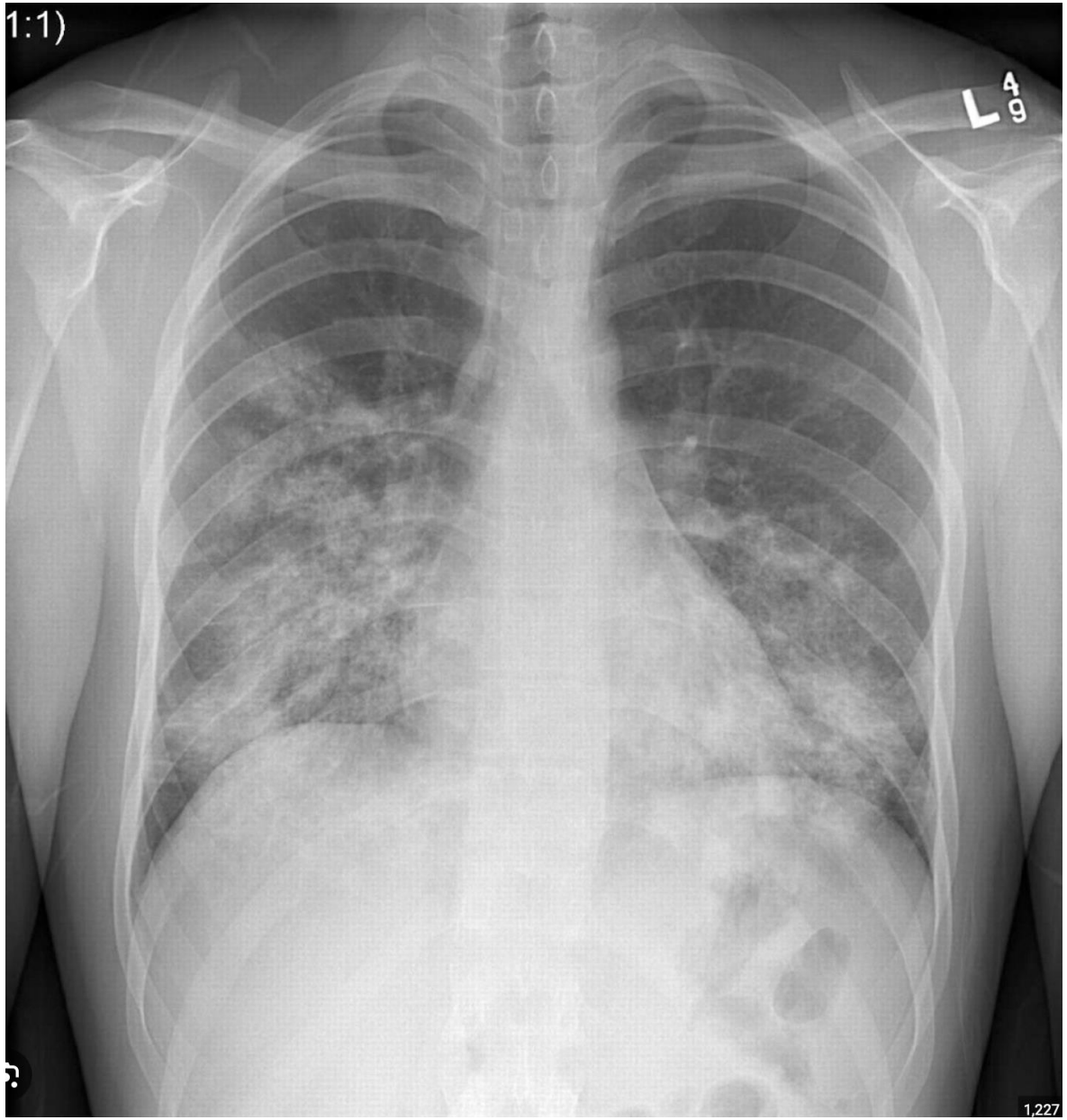
Madame D, femme de 57 ans, connue:

- **Granulomatose avec polyangéite**
  - sp tx avec cyclophosphamide x10 ans (inefficace), methotrexate + azathioprine (cessé pour cérébrite), présentement traitée avec:
    - Rituximab 500 mg IV q6 mois (dernière dose 16 mars 2022)
    - Methotrexate 25 mg sc q1 semaine
    - Prednisone 5 mg PO DIE
- Otites à répétition, déficit vestibulaire (neuronite vestibulaire vs GPA), hypoacousie neurosensorielle, s/p exérèse mucocèle narine G (2019)
- Adénite lithiasique sous maxillaire D
- Bronchites virales
- Lymphopénie chronique
- HypoT4, anémie normocytaire, ostéoporose, fractures traumatiques poignet et costale D
- Vaccinée COVID x4 (dernière dose 15 février 2022)

Présentation du cas

Madame D, femme de 57 ans:

- Dyspnée progressive, toux, myalgies, anosmie: test COVID positif 10 avril 2022 (jour 0)
- Traitements:
  - Sotrovimab en clinique externe jour 4
  - Azithromycine jour 18
  - Lévofloxacin jour 41
- Référée à l'hospitalisation pour dyspnée et fièvre persistantes



Début de pipéracilline-tazobactam empirique

Tests COVID positifs:

- PCR
- Sérologie IgG anti-spike (NADAL-COVID)

Question 1

Nommer 3 tests dans l'investigation initiale de cette patiente

- Scan thoracique: opacités alvéolaires et en verre dépoli multi-focales, pas de nodules parenchymateux suggérant flare-up vasculite
- ANCA négatifs
- Cultures d'expectorations préliminaires négatives

Le lendemain…

- CRP 134 → 233
- Début de besoins d'oxygène ad 1.5 L/min
- Augmentation des infiltrats au RXP

Question 2

Nommer 2 tests dans l'investigation complémentaire de cette patiente

- Angioscan: pas d'embolie pulmonaire, progression des infiltrats
- Bronchoscopie:
  - Pas d'hémorragie alvéolaire
  - Cultures de bactéries et virus communs, germes opportunistes négatives

Question 3

Nommer 3 champignons opportunistes à éliminer chez cette patiente:

Diagnostic différentiel de la fièvre et infiltrats pulmonaires chez les immunosupprimés

Infectieux	Non-infectieux
Bactérien (bactéries “conventionnelles” 37%)	Surcharge
Viral: CMV, VZV, HSV (15%)	Embolie pulmonaire
Tuberculose	Néoplasie
Fongiques: aspergillus, PCP, cryptococcus (14%)	Auto-immun: connectivite, vasculite ANCA (hémorragie alvéolaire), OP, fibrose pulmonaire, sarcoidose
Parasites: strongyloïdes, toxoplasmose	Médicamenteux: - Hypersensibilité aigue: MTX, cyclophosphamide, bléomycine, etc. - Réaction à doses accumulées (chimio)
Nocardia (7%)	
Mixtes (20%)	

Question 4

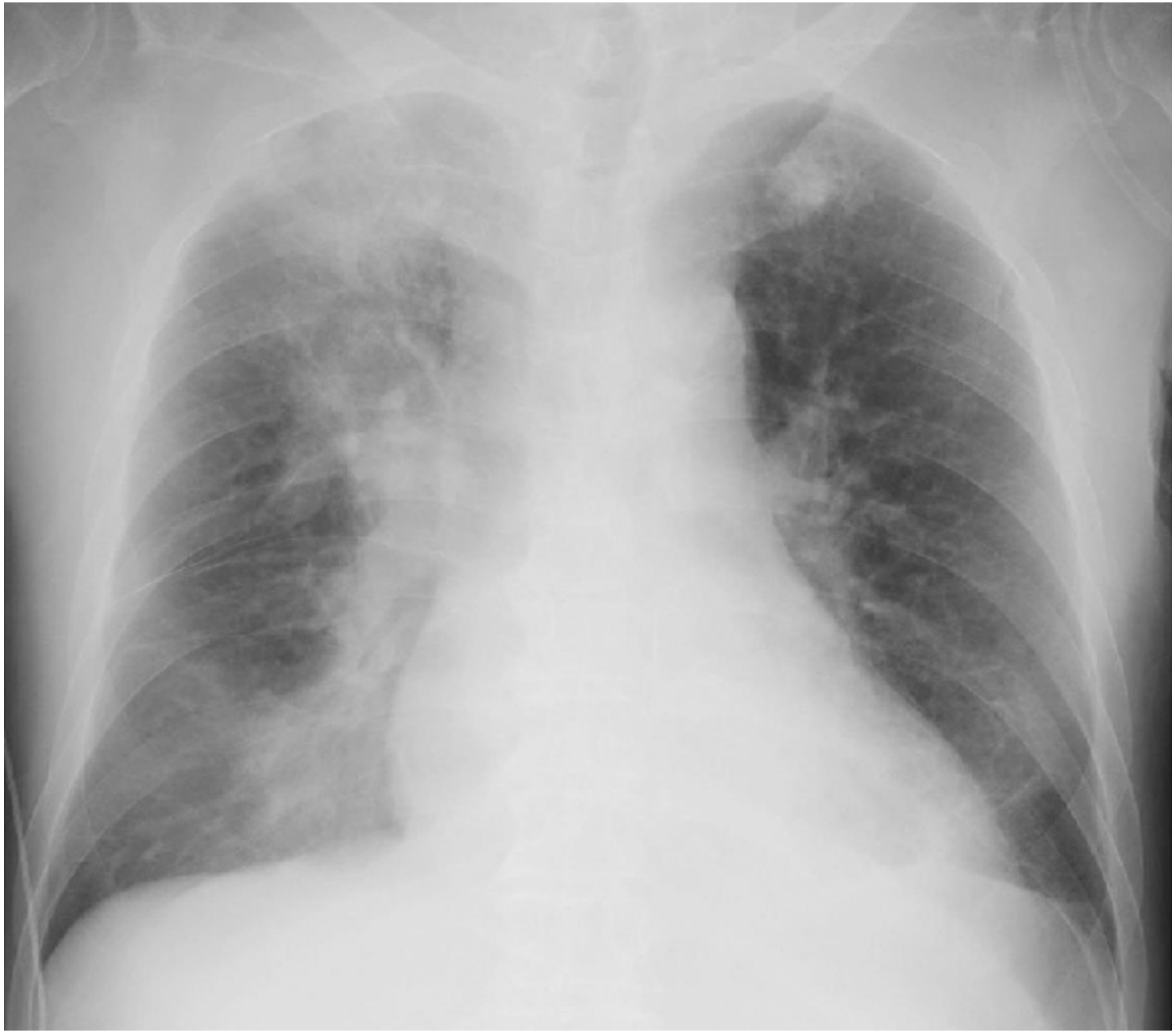
À la lumière des résultats d'investigation, quel est le principal pathogène causatif du tableau, et quel sont les traitements à initier?

Après 10 jours de traitement…

- CRP <10
- Résolution de la fièvre, de l'hypoxémie et de la dyspnée
- Congé

5 jours après le congé…

- Revient à l’urgence pour DEG, fièvre et toux
- CRP 162
- PCR COVID positif



PCR COVID positif

Question 5

Quels sont les diagnostics les plus probables à ce stade-ci?

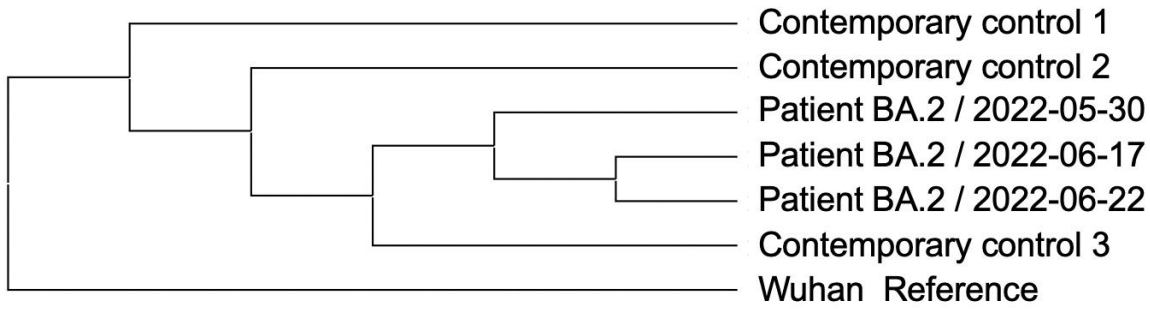
- Surinfection bactérienne nouvelle
- COVID
  - Ré-infection
  - Persistance

Confirmation de COVID persistante avec séquençage viral génomique

A.

	Wuhan Reference	Patient BA.2 / 2022-05-30	Patient BA.2 / 2022-06-17	Patient BA.2 / 2022-06-22
Wuhan Reference	0			
Patient BA.2 / 2022-05-30	47	0		
Patient BA.2 / 2022-06-17	70	1	0	
Patient BA.2 / 2022-06-22	44	2	1	0

B.



Traitement d’une COVID persistante

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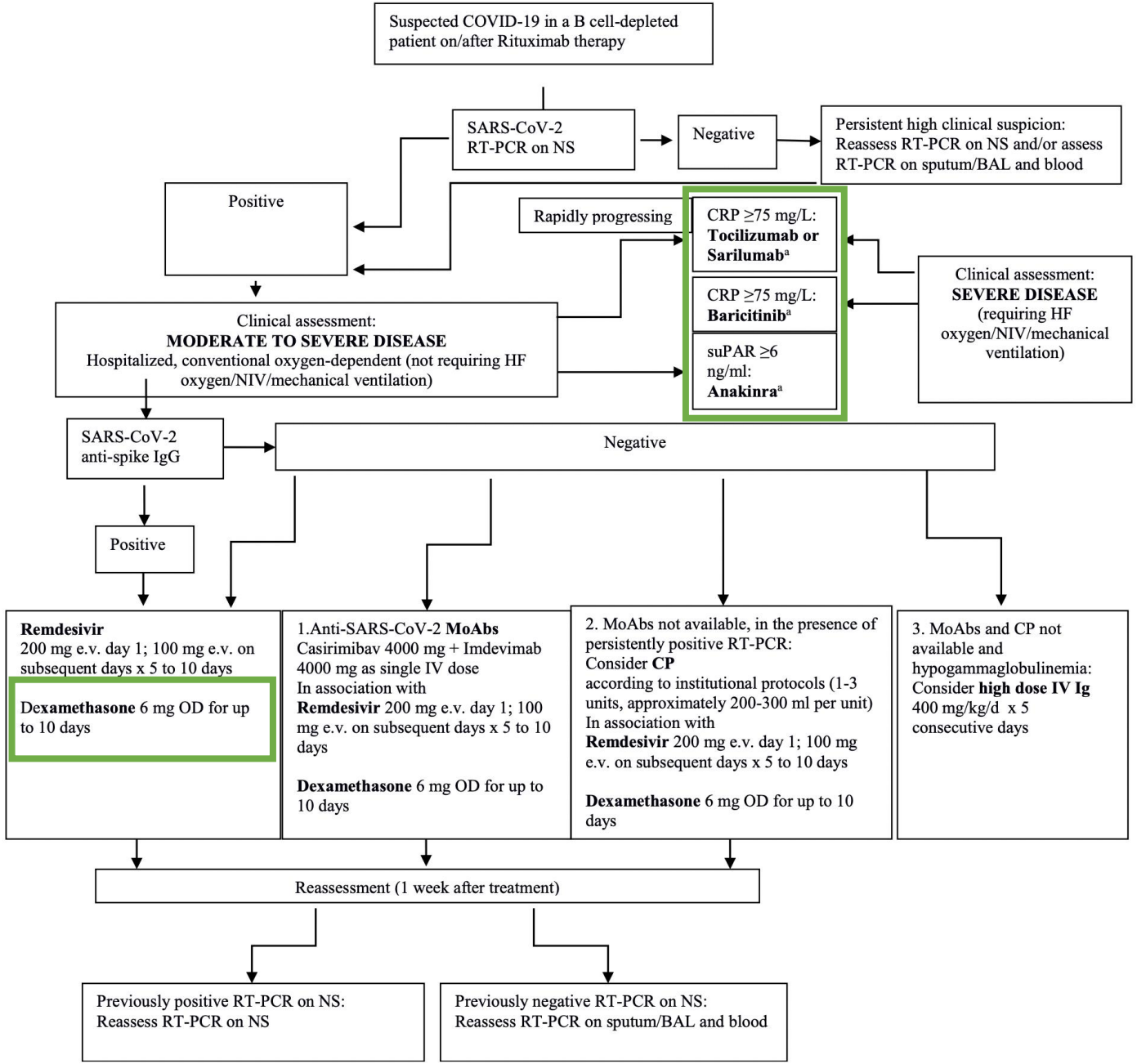
B



1) Prévention de la détérioration
   a) Réduction de l'hyperinflammation
      i. Anti-IL6: tocilizumab, sarilumab
      ii. Anti-TNF alpha: Baricitinib
      iii. Anti-IL1: Anakinra
      iv. Dexaméthasone
   b) Prévention thromboembolique

Case report

COVID-19 in a MS patient treated with ocrelizumab: does immunosuppression have a protective role?

Giovanni Novi[a], Malgorzata Mikulska[b,c], Federica Briano[b,c], Federica Toscanini[c], Francesco Tazza[c,d], Antonio Uccelli[c,d], Matilde Inglese[c,d,*]

[a] *Department of Neuroscience, Ospedale Policlinico San Martino, IRCCS, Genova, Italy*
[b] *Department of Health Sciences (DISSAL), University of Genova, Genova, Italy*
[c] *Ospedale Policlinico San Martino, IRCCS, Genova, Italy*
[d] *Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI) and Center of Excellence for Biomedical Research (CEBR), University of Genova, Genova, Italy*

A B S T R A C T

Background: Coronavirus disease 19 (COVID-19) is a novel disease entity that is spreading throughout the world. It has been speculated that patients with co-morbidities and elderly patients could be at high risk for respiratory insufficiency and death. Immunosuppression could expose infected patients to even higher risks of disease complications due to dampened immune response. However, it has been speculated that overactive immune response could drive clinical deterioration and, based on this hypothesis, several immunosuppressants are currently being tested as potential treatment for COVID-19.
Methods: In this paper we report on a patient that has been treated with ocrelizumab (a B-cell depleting monoclonal antibody) for primary progressive multiple sclerosis who developed COVID-19.
Results: Despite complete B cell depletion, patient symptoms abated few days after hospitalization, and he was discharged to home-quarantine. Phone interview follow-up confirmed that, after 14 days, no new symptoms occurred.
Discussion: This report supports the putative role of immunosuppressive therapy in COVID-19 affected patients.

Case Report

Unexpected Positive Effects of Rituximab and Corticosteroids on COVID-19 in a Patient Suffering from Granulomatosis with Polyangiitis

Abstract

The COVID-19 pandemic has raised concerns among physicians and patients with autoimmune disorders about how this viral infection affects the patients receiving immunosuppressive drugs. There are speculations about a higher incidence and severity of COVID-19 in patients receiving a variety of immunosuppressant drugs. However, we reported the rapid recovery from COVID-19 in a 67-year-old male with granulomatosis with polyangiitis who did not experience severe symptoms of the COVID-19 as expected, despite having a history of serious lung involvement due to the autoimmune disease. He received conventional medications to treat COVID-19, though he had been receiving rituximab and corticosteroids before the onset of COVID-19 symptoms. Prevention of the cytokine storm caused by SARS-CoV-2 infection owing to taking the immunosuppressive drugs (rituximab and corticosteroids) could be a reason for these unexpected observations. Therefore, this case showed that taking immunosuppressive drugs is unlikely to be directly related to the increased severity of COVID-19.

Keywords: *COVID-19, cytokine storm, granulomatosis with polyangiitis, immunosuppressive drugs, rituximab*

Mansour Salesi[1,2], Behrokh Shojaie[1,2], Zohre Naderi[1]

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La diminution de l'immunité humorale diminue-t-elle aussi l'hyper-inflammation reliée aux infections COVID sévères?

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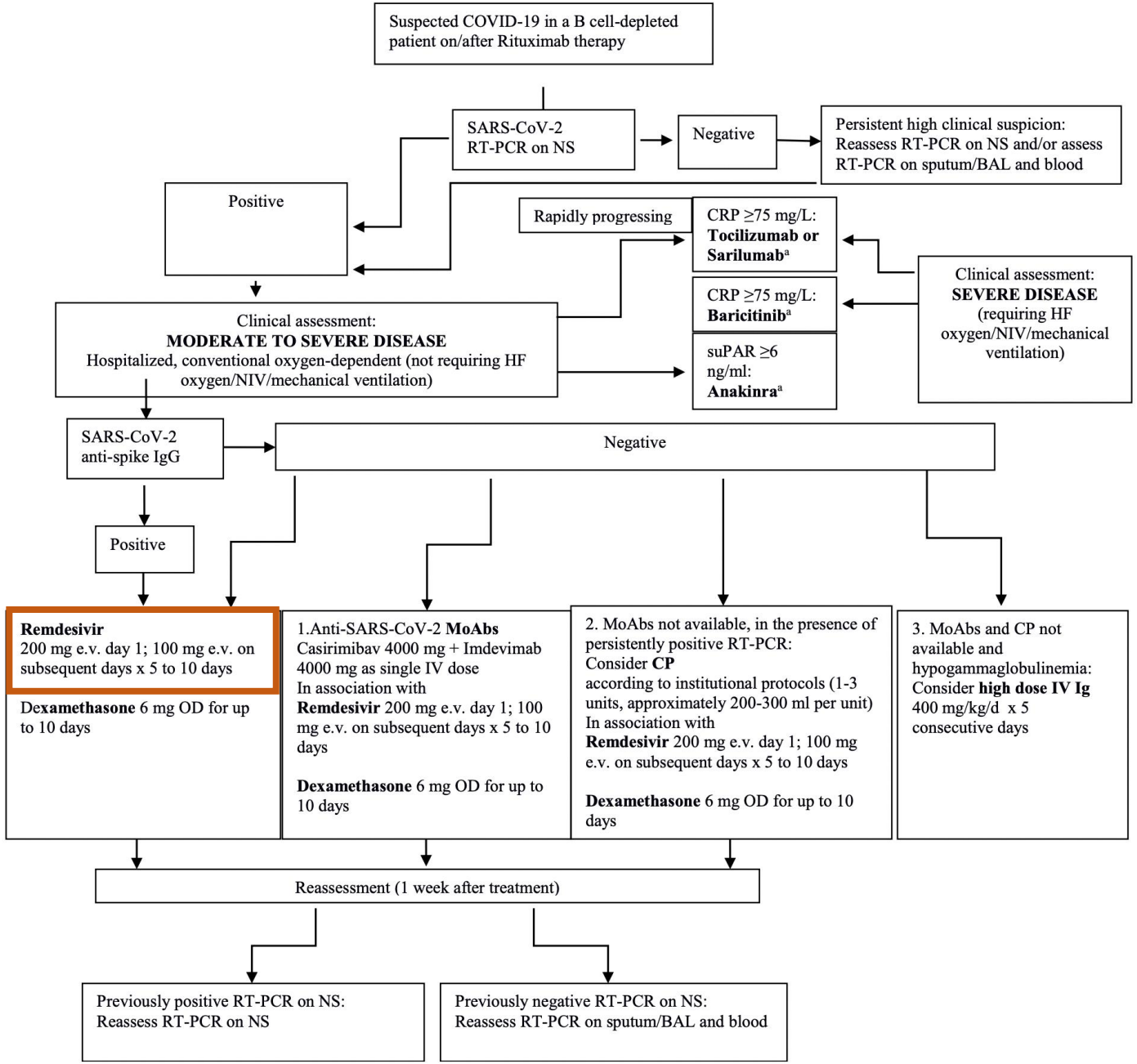

1) Prévention de la détérioration
   a) Réduction de l'hyperinflammation
      i. Anti-IL6: tocilizumab, sarilumab
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      iv. Dexaméthasone
   b) Prévention thromboembolique
2) Clairance virale
   a) Analogue de nucléosides: remdesivir

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ESTABLISHED IN 1812 NOVEMBER 5, 2020 VOL. 383 NO. 19

Remdesivir for the Treatment of Covid-19 — Final Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

ABSTRACT

BACKGROUND

Although several therapeutic agents have been evaluated for the treatment of coronavirus disease 2019 (Covid-19), no antiviral agents have yet been shown to be efficacious.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only.

RESULTS

A total of 1062 patients underwent randomization (with 541 assigned to remdesivir and 521 to placebo). Those who received remdesivir had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), as compared with 15 days (95% CI, 13 to 18) among those who received placebo (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; P<0.001, by a log-rank test). In an analysis that used a proportional-odds model with an eight-category ordinal scale, the patients who received remdesivir were found to be more likely than those who received placebo to have clinical improvement at day 15 (odds ratio, 1.5; 95% CI, 1.2 to 1.9, after adjustment for actual disease severity). The Kaplan–Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Serious adverse events were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%).

CONCLUSIONS

Our data show that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. (Funded by the National Institute of Allergy and Infectious Diseases and others; ACTT-1 ClinicalTrials.gov number, NCT04280705.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Beigel at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, 5601 Fishers Ln., Rm. 7E60, MSC 9826, Rockville, MD 20892-9826, or at jbeigel@niaid.nih.gov.

*A complete list of members of the ACTT-1 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

A preliminary version of this article was published on May 22, 2020, at NEJM.org. This article was published on October 8, 2020, and updated on October 9, 2020, at NEJM.org.

N Engl J Med 2020;383:1813-26.
DOI: 10.1056/NEJMoa2007764

Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial

Canadian Treatments for COVID-19 (CATCO)*; for the Association of Medical Microbiology and Infectious Disease Canada (AMMI) Clinical Research Network and the Canadian Critical Care Trials Group

*The complete list of authors appears at the end of the article.

■ Cite as: *CMAJ* 2022 February 22;194:E242-51.doi: 10.1503/cmaj.211698; early-released January 19, 2022

Abstract

Background: The role of remdesivir in the treatment of patients in hospital with COVID-19 remains ill defined in a global context. The World Health Organization Solidarity randomized controlled trial (RCT) evaluated remdesivir in patients across many countries, with Canada enrolling patients using an expanded data collection format in the Canadian Treatments for COVID-19 (CATCO) trial. We report on the Canadian findings, with additional demographics, characteristics and clinical outcomes, to explore the potential for differential effects across different health care systems.

Methods: We performed an open-label, pragmatic RCT in Canadian hospitals, in conjunction with the Solidarity trial. We randomized patients to 10 days of remdesivir (200 mg intravenously [IV] on day 0, followed by 100 mg IV daily), plus standard care, or standard care alone. The primary outcome was in-hospital mortality. Secondary outcomes included changes in clinical severity, oxygen- and ventilator-free days (at 28 d), incidence of new oxygen or mechanical ventilation use, duration of hospital stay, and adverse event rates. We performed a priori subgroup analyses according to duration of symptoms before enrolment, age, sex and severity of symptoms on presentation.

Results: Across 52 Canadian hospitals, we randomized 1282 patients between Aug. 14, 2020, and Apr. 1, 2021, to remdesivir (n = 634) or standard of care (n = 648). Of these, 15 withdrew consent or were still in hospital, for a total sample of 1267 patients. Among patients assigned to receive remdesivir, in-hospital mortality was 18.7%, compared with 22.6% in the standard-of-care arm (relative risk [RR] 0.83 (95% confidence interval [CI] 0.67 to 1.03), and 60-day mortality was 24.8% and 28.2%, respectively (95% CI 0.72 to 1.07). For patients not mechanically ventilated at baseline, the need for mechanical ventilation was 8.0% in those assigned remdesivir, and 15.0% in those receiving standard of care (RR 0.53, 95% CI 0.38 to 0.75). Mean oxygen-free and ventilator-free days at day 28 were 15.9 (± standard deviation [SD] 10.5) and 21.4 (± SD 11.3) in those receiving remdesivir and 14.2 (± SD 11) and 19.5 (± SD 12.3) in those receiving standard of care (p = 0.006 and 0.007, respectively). There was no difference in safety events of new dialysis, change in creatinine, or new hepatic dysfunction between the 2 groups.

Interpretation: Remdesivir, when compared with standard of care, has a modest but significant effect on outcomes important to patients and health systems, such as the need for mechanical ventilation. **Trial registration**: ClinicalTrials.gov, no. NCT04330690.

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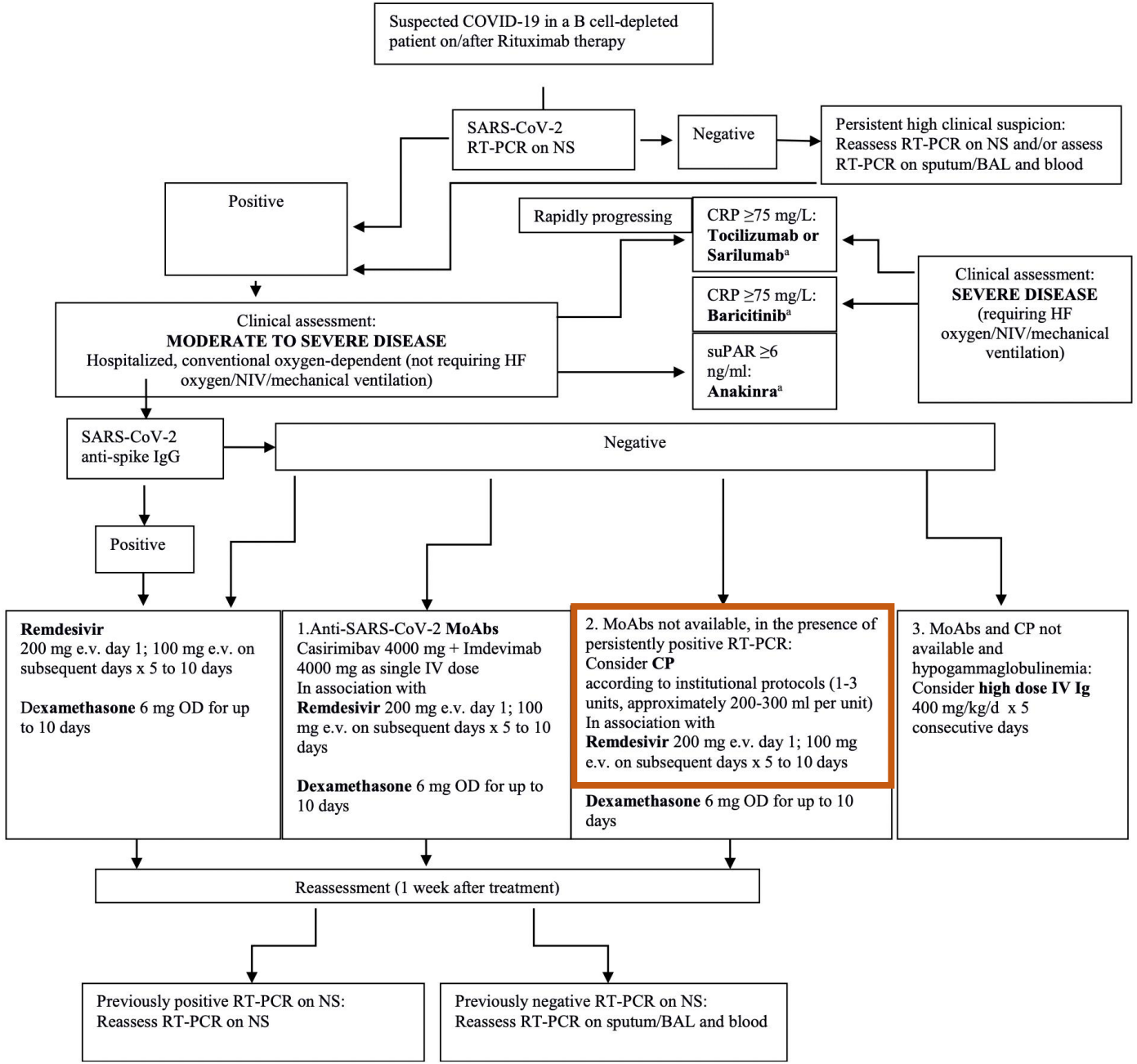

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      ii. Anti-TNF alpha: Baricitinib
      iii. Anti-IL1: Anakinra
      iv. Dexaméthasone
   b) Prévention thromboembolique
2) Clairance virale
   a) Analogue de nucléosides: remdesivir
   b) Immunité passive
      i. Plasma convalescent

ORIGINAL ARTICLE

Early Convalescent Plasma for High-Risk Outpatients with Covid-19

F.K. Korley, V. Durkalski-Mauldin, S.D. Yeatts, K. Schulman, R.D. Davenport, L.J. Dumont, N. El Kassar, L.D. Foster, J.M. Hah, S. Jaiswal, A. Kaplan, E. Lowell, J.F. McDyer, J. Quinn, D.J. Triulzi, C. Van Huysen, V.L.W. Stevenson, K. Yadav, C.W. Jones, B. Kea, A. Burnett, J.C. Reynolds, C.F. Greineder, N.L. Haas, D.G. Beiser, R. Silbergleit, W. Barsan, and C.W. Callaway, for the SIREN-C3PO Investigators*

ABSTRACT

BACKGROUND

Early administration of convalescent plasma obtained from blood donors who have recovered from coronavirus disease 2019 (Covid-19) may prevent disease progression in acutely ill, high-risk patients with Covid-19.

METHODS

In this randomized, multicenter, single-blind trial, we assigned patients who were being treated in an emergency department for Covid-19 symptoms to receive either one unit of convalescent plasma with a high titer of antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or placebo. All the patients were either 50 years of age or older or had one or more risk factors for disease progression. In addition, all the patients presented to the emergency department within 7 days after symptom onset and were in stable condition for outpatient management. The primary outcome was disease progression within 15 days after randomization, which was a composite of hospital admission for any reason, seeking emergency or urgent care, or death without hospitalization. Secondary outcomes included the worst severity of illness on an 8-category ordinal scale, hospital-free days within 30 days after randomization, and death from any cause.

RESULTS

A total of 511 patients were enrolled in the trial (257 in the convalescent-plasma group and 254 in the placebo group). The median age of the patients was 54 years; the median symptom duration was 4 days. In the donor plasma samples, the median titer of SARS-CoV-2 neutralizing antibodies was 1:641. Disease progression occurred in 77 patients (30.0%) in the convalescent-plasma group and in 81 patients (31.9%) in the placebo group (risk difference, 1.9 percentage points; 95% credible interval, −6.0 to 9.8; posterior probability of superiority of convalescent plasma, 0.68). Five patients in the plasma group and 1 patient in the placebo group died. Outcomes regarding worst illness severity and hospital-free days were similar in the two groups.

CONCLUSIONS

The administration of Covid-19 convalescent plasma to high-risk outpatients within 1 week after the onset of symptoms of Covid-19 did not prevent disease progression. (SIREN-C3PO ClinicalTrials.gov number, NCT04355767.)

ORIGINAL ARTICLE

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

V.A. Simonovich, L.D. Burgos Pratx, P. Scibona, M.V. Beruto, M.G. Vallone, C. Vázquez, N. Savoy, D.H. Giunta, L.G. Pérez, M..L. Sánchez, A.V. Gamarnik, D.S. Ojeda, D.M. Santoro, P.J. Camino, S. Antelo, K. Rainero, G.P. Vidiella, E.A. Miyazaki, W. Cornistein, O.A. Trabadelo, F.M. Ross, M. Spotti, G. Funtowicz, W.E. Scordo, M.H. Losso, I. Ferniot, P.E. Pardo, E. Rodriguez, P. Rucci, J. Pasquali, N.A. Fuentes, M. Esperatti, G.A. Speroni, E.C. Nannini, A. Matteaccio, H.G. Michelangelo, D. Follmann, H.C. Lane, and W.H. Belloso, for the PlasmAr Study Group*

ABSTRACT

BACKGROUND

Convalescent plasma is frequently administered to patients with Covid-19 and has been reported, largely on the basis of observational data, to improve clinical outcomes. Minimal data are available from adequately powered randomized, controlled trials.

METHODS

We randomly assigned hospitalized adult patients with severe Covid-19 pneumonia in a 2:1 ratio to receive convalescent plasma or placebo. The primary outcome was the patient's clinical status 30 days after the intervention, as measured on a six-point ordinal scale ranging from total recovery to death.

RESULTS

A total of 228 patients were assigned to receive convalescent plasma and 105 to receive placebo. The median time from the onset of symptoms to enrollment in the trial was 8 days (interquartile range, 5 to 10), and hypoxemia was the most frequent severity criterion for enrollment. The infused convalescent plasma had a median titer of 1:3200 of total SARS-CoV-2 antibodies (interquartile range, 1:800 to 1:3200). No patients were lost to follow-up. At day 30 day, no significant difference was noted between the convalescent plasma group and the placebo group in the distribution of clinical outcomes according to the ordinal scale (odds ratio, 0.83 (95% confidence interval [CI], 0.52 to 1.35; P=0.46). Overall mortality was 10.96% in the convalescent plasma group and 11.43% in the placebo group, for a risk difference of –0.46 percentage points (95% CI, –7.8 to 6.8). Total SARS-CoV-2 antibody titers tended to be higher in the convalescent plasma group at day 2 after the intervention. Adverse events and serious adverse events were similar in the two groups.

CONCLUSIONS

No significant differences were observed in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo. (PlasmAr ClinicalTrials.gov number, NCT04383535.)

Case Report

Dramatic Response to Convalescent Hyperimmune Plasma in Association With an Extended Course of Remdesivir in 4 B Cell–Depleted Non-Hodgkin Lymphoma Patients With SARS-Cov-2 Pneumonia After Rituximab Therapy

Anna Furlan,[1] Gabriella Forner,[2] Ludovica Cipriani,[2] Elisa Vian,[3] Roberto Rigoli,[3] Filippo Gherlinzoni,[1] Piergiorgio Scotton[2]

Clinical Practice Points

- Four B cell–depleted non-Hodgkin lymphoma (NHL) patients with SARS-CoV-2 pneumonia after rituximab therapy were initially treated with a 5-day remdesivir course and steroids. After transient virologic and clinical response, they all experienced early relapse and subsequent prolonged disease course, with rapid and significant response to convalescent hyperimmune plasma in association with an extended course of remdesivir. The clinical observations here reported suggest that the immunological effects of Rituximab treatment in NHL patients should be taken into account for the proper choice and interpretation of SARS-CoV-2 laboratory tests and to guide the appropriate therapeutical approach.

Clinical Lymphoma, Myeloma and Leukemia, Vol. 21, No. 9, e731–e735
Keywords: SARS-CoV-2, non-Hodgkin lymphoma, Rituximab, B cell depletion convalescent hyperimmune plasma remdesivir

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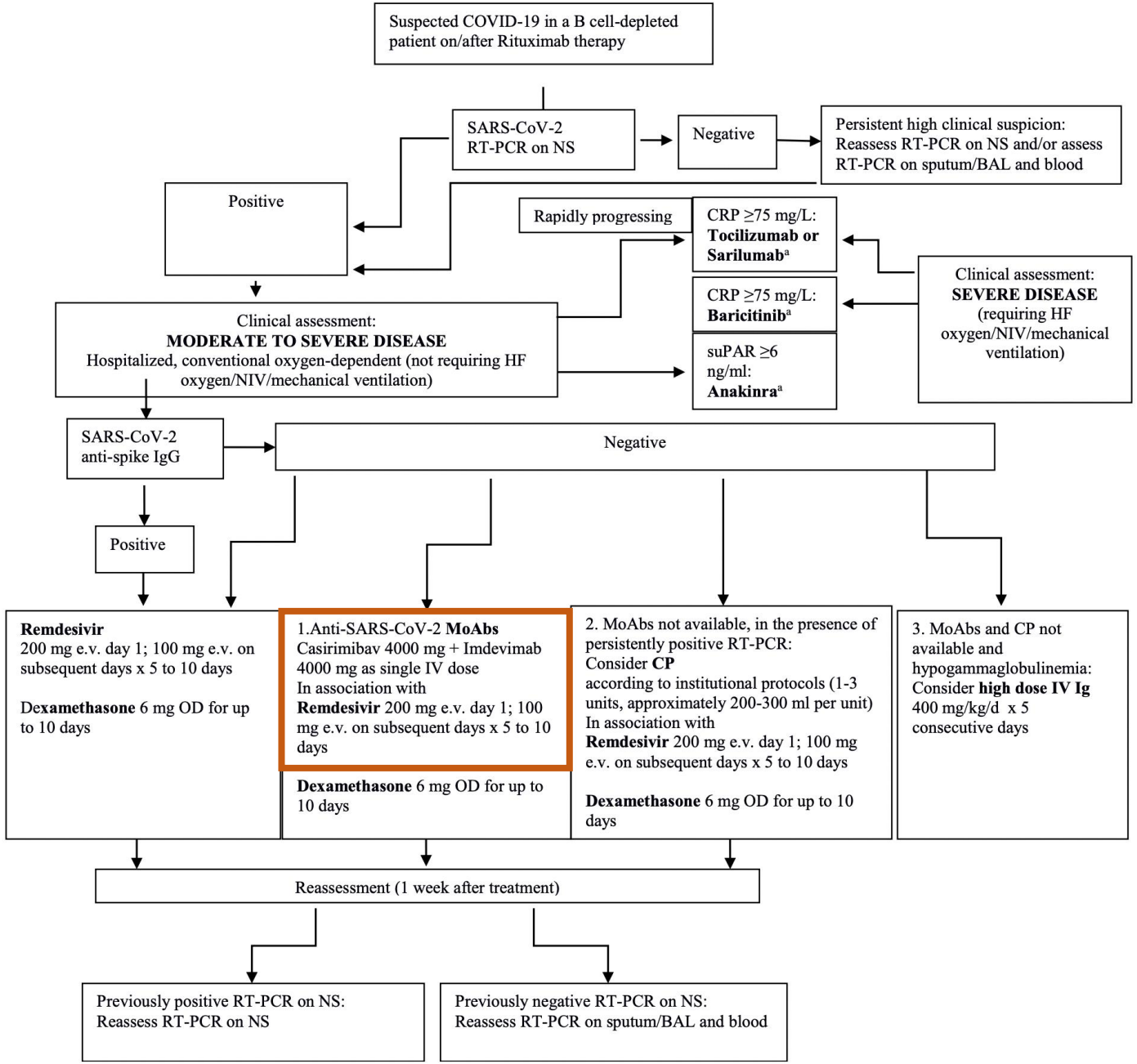

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      iv. Dexaméthasone
   b) Prévention thromboembolique
2) Clairance virale
   a) Analogue de nucléosides: remdesivir
   b) Immunité passive
      i. Plasma convalescent
      ii. Anticorps monoclonaux (anti-spike): sotrovimab, casirimibav-imdevimab, tixagevimab-cilgavimab…

Article

Antibody evasion properties of SARS-CoV-2 Omicron sublineages

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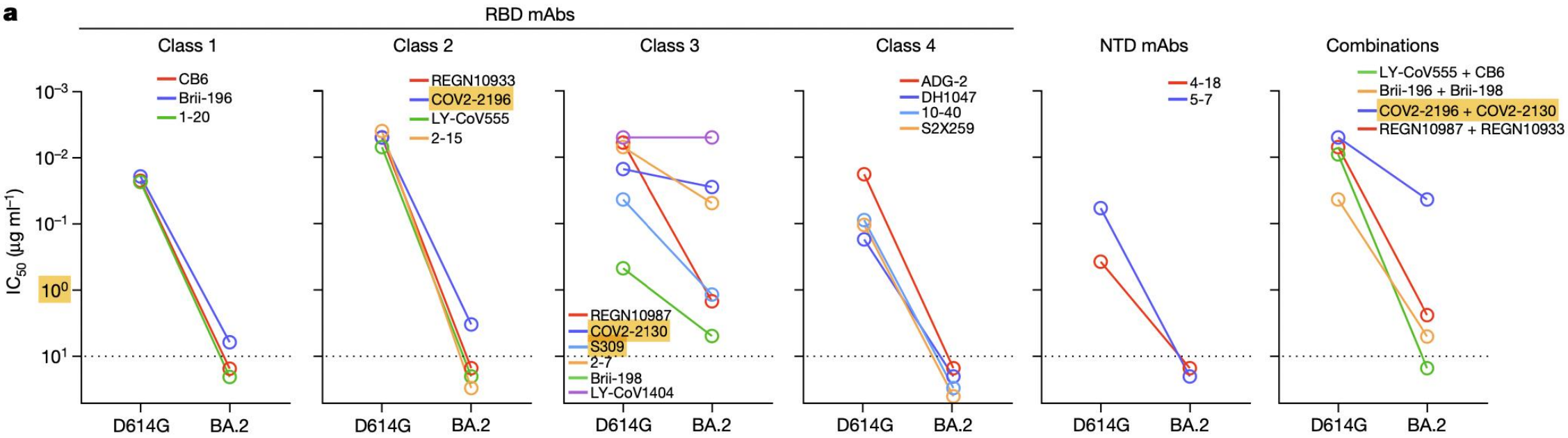
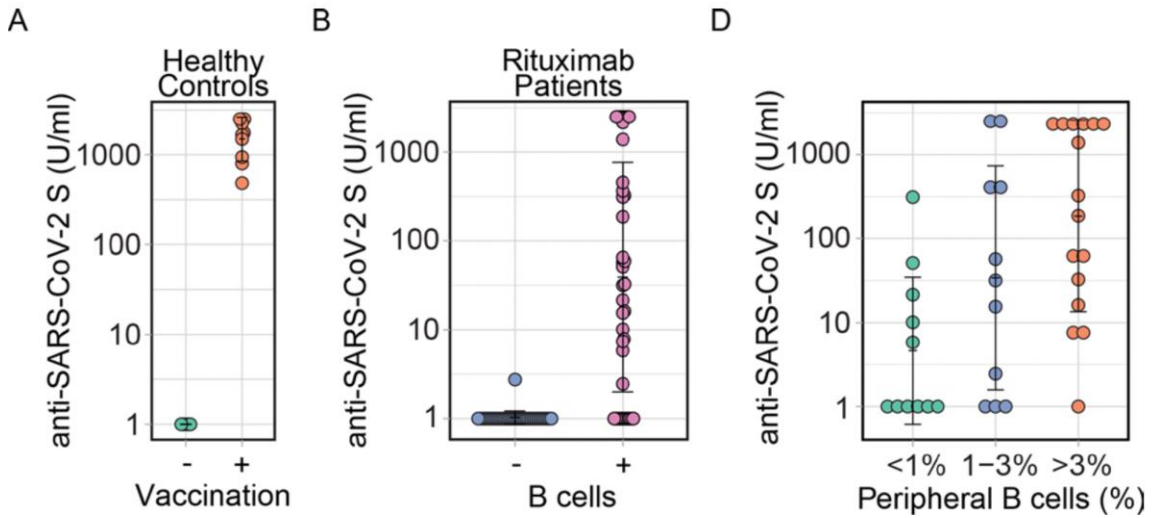
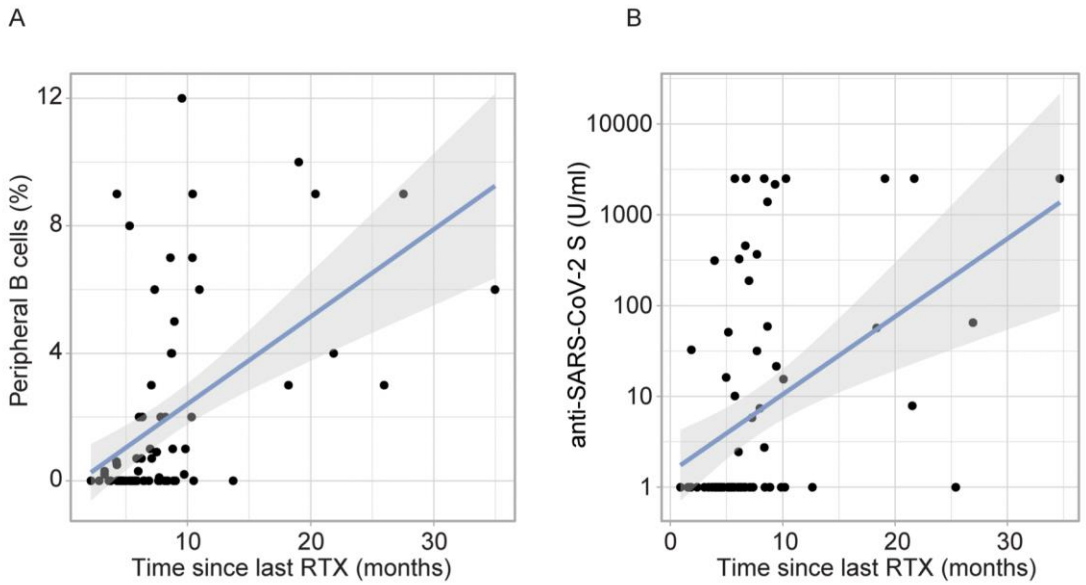
Sho Iketani[1,2,8], Lihong Liu[1,8], Yicheng Guo[1,8], Liyuan Liu[3,8], Jasper F.-W. Chan[4,5,8], Yiming Huang[3], Maple Wang[1], Yang Luo[1], Jian Yu[1], Hin Chu[4,5], Kenn K.-H. Chik[4,5], Terrence T.-T. Yuen[4], Michael T. Yin[1,6], Magdalena E. Sobieszczyk[1,6], Yaoxing Huang[1], Kwok-Yung Yuen[4,5], Harris H. Wang[3,7], Zizhang Sheng[1] & David D. Ho[1,2,6]✉



1) Suivi des patterns de résistance dans l'évolution des souches virales
2) Combinaison d'Ac monoclonaux

Quand redonner le rituximab?





Quand redonner le rituximab?

- Équilibre entre immunosuppression et clairance virale/ prévention d'une nouvelle infection
- Suspendre le rituximab jusqu'à l'obtention d'un PCR négatif

Retour à Mme D.

- Administration d'une 1ère dose de tixagevimab-cilgavimab (Evusheld) à la fin de sa 2e hospitalisation
- Pas d'autres récidives de symptômes, obtention d'un PCR SARS-CoV2 négatif 115 jours après son 1er test positif
- Suspension de sa dose de rituximab prévue en septembre 2022 (3 mois après hospitalisation)
- 2e dose de tixagevimab-cilgavimab (Evusheld) en décembre 2022

Messages-clés

Chez les patients immunosupprimés, particulièrement ceux avec déplétion de cellules B:

1. La COVID persistante devrait être rapidement suspectée chez les patients ayant eu une infection COVID récente et des symptômes récidivants ou persistants
2. La clairance virale semble dépendre de l'administration d'une immunité passive, incluant les anticorps monoclonaux anti-SARS-CoV2

Merci pour votre attention!

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