Recommendations

ERN ReCONNET points to consider for treating patients living with autoimmune rheumatic diseases with antiviral therapies and anti-SARS-CoV-2 antibody products

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Funding information and competing interests on page 8.

ABSTRACT

Recent studies have shown that people who are immunocompromised may inadvertently play a role in spurring the mutations of the virus that create new variants. This is because some immunocompromised individuals remain at risk of getting COVID-19 despite vaccination, experience more severe disease, are susceptible to being chronically infected and remain contagious for longer if they become infected and considering that immunocompromised individuals represent approximately 2% of the overall population, this aspect should be carefully considered.

So far, some autoimmune rheumatic disease (ARD) patients with COVID-19 have been treated with antiviral therapies or anti-SARS-CoV-2 antibody products. However, there is no homogeneous approach to these treatment strategies. This issue was addressed within the European Reference Network (ERN) on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ReCONNET) in a discussion among experts and patient's representatives in the context of the rare and complex connective tissue diseases (rCTDs) covered by the Network. ERN ReCONNET is one of the 24 ERNs launched by the European Commission in 2017 with the aim of tackling low prevalence and rare diseases that require highly specialised treatment and promoting concentration of knowledge and resources through virtual networks involving healthcare providers (HCPs) across the European Union (EU).

Considering the urgent need to provide guidance not only to the rCTDs community, but also to the whole ARDs community, a multidisciplinary Task Force, including expert clinicians and European Patient Advocacy Group (ePAG) Advocates, was created in the framework of ERN ReCONNET with the aim of developing overarching principles (OP) and points-to-consider (PtC) on a homogenous approach to treat immunocompromised patients with ARDs (with a particular focus on CTDs) affected by COVID-19 using antiviral therapies and anti-SARS-CoV-2 antibody products. The present work reports the final OP and PtC agreed by the Task Force.

- *What is already known about this subject?*
  Immunocompromised individuals remain at risk of getting COVID-19 despite vaccination, may be susceptible to being chronically infected, and remain contagious for longer if they become infected.
- *What does this study add?*
  The present overarching principles (OP) and points-to-consider (PtC) aim at facilitating a homogenous approach to treat immunocompromised patients with ARDs affected by COVID-19 using antiviral therapies and anti-SARS-CoV-2 antibody products.
- *How might this impact clinical practice?*
  The PtC highlight how booster and pre-exposure treatment can be considered complementary, as well as the need to early use antiviral agents and ant- SARS-CoV-2 antibody products in most fragile patients.

Introduction

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused significant morbidity and mortality and stressed healthcare systems worldwide (1). The COVID-19 vaccination campaign has substantially altered the course of the pandemic, saving millions of lives globally. Ensuring that as many people as possible are protected from SARS-CoV-2 is crucial for preventing the infection as well as the emergence of new variants (2).

Whether patients with autoimmune rheumatic diseases (ARDs) are at increased risk for adverse COVID-19 outcomes due to the underlying chronic disease, or to the ongoing immunosuppressive treatments and comorbidities is still matter of debate (3, 4). In addition, patients with ARDs have shown a reduced immunogenicity of anti-SARS-CoV-2 vaccines compared with healthy controls (5) especially if concomitantly treated with rituximab, abatacept, methotrexate, mycophenolate mofetil, or high doses of glucocorticoids. Administration of a booster dose of COVID-19 vaccine is, therefore, of particular importance in these patients to restore a protective antibody titre (5).

Recent studies have shown that people who are immunocompromised may inadvertently play a role in spurring the mutations of the virus that create new variants (6, 7). This is because some immunocompromised individuals remain at risk of getting COVID-19 despite vaccination, experience more severe disease, are susceptible to being chronically infected and remain contagious for longer if they become infected (8-9). For instance, a study from Israel showed that more than 40% of people hospitalised with breakthrough infections after vaccination were immunocompromised (10). In addition, patients affected by ARDs may be susceptible to prolonged COVID-19 symptoms; recent data have demonstrated that about 1/4 of ARDs patients experienced COVID-19 symptoms duration of 28 days or longer and 1/10 experienced symptoms 90 days or longer (11). Considering that immunocompromised individuals represent approximately 2% of the overall population, this aspect should be carefully considered.

So far, some ARDs patients with COVID-19 have been treated with antiviral therapies or anti-SARS-CoV-2 antibody products. However, there is no homogeneous approach to these treatment strategies. This issue was addressed within the European Reference Network (ERN) on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ReCONNET) (12) in a discussion among experts and patient's representatives in the context of the rare and complex connective tissue diseases (rCTDs) covered by the Network. ERN ReCONNET is one of the 24 ERNs launched by the European Commission in 2017 with the aim of tackling low prevalence and rare diseases that require highly specialised treatment and promoting concentration of knowledge and resources through virtual networks involving healthcare providers (HCPs) across the European Union (EU). This ERN acts as a European infrastructure to support patients with rare and complex diseases, recognising that the best way of delivering care to these patients is through the sharing of experience and knowledge in the context of a network (13). To date, ERN ReCONNET counts 55 Full Members and 9 Affiliated Partners over 23 European countries (Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovenia, Spain, Sweden, and The Netherlands).

Considering the urgent need to provide guidance not only to the rCTDs community, but also to the whole ARDs community, a multidisciplinary Task Force, including expert clinicians and European Patient Advocacy Group (ePAG) Advocates, was created in the framework of ERN ReCONNET with the aim of developing overarching principles (OP) and points-to-consider (PtC) on a homogenous approach to treat immunocompromised patients with ARDs (with a particular focus on CTDs) affected by COVID-19 using antiviral therapies and anti-SARS-CoV-2 antibody products. The present work reports the final OP and PtC agreed by the Task Force.

Methods

The Task Force

After approval by the ERN ReCONNET Steering Committee of the submitted by the convenor (MM) and the co-convenor (RT) proposal, a Task Force was established, composed by a Restricted Task Force and an Extended Task Force group.

The Restricted Task Force was composed by the convenors, a methodologist (RT, the co-convenor), four fellows (GAR, SB, CC, PT, who are members of the ERN ReCONNET Young Working Group) and members of the ERN ReCONNET Expert Panel on Clinical Practice Guidelines and Clinical-Decision Support Tools (GB, AB, LD, IG, LI, AM, CP, VCR, CAS, VS, AS, CT, DM). Furthermore, a call for interest was launched across all the centres of the Network and the ePAG Advocates in order to implement the Extended Task Force.

Globally, the Extended Task Force was composed by 46 clinicians, including an infectious disease specialist and a virologist), four ePAG Advocates and one Network manager.

Two online Task Force meetings were held; the first in October 2022, during which the Restricted Task Force agreed on the protocol and on the research questions. After that, the systematic literature review (SLR) was conducted by the four fellows and guided by the methodologist. A second Task Force online meeting took place in November 2022, comprising the Extended Task Force and aimed at discussing the results of the SLR and the preliminary OP and PtC provided on the basis of the SLR and the experts' opinion.

Target audience

The primary target audience of the present OP and PtC is represented by healthcare professionals (HCPs) taking care of ARDs patients and patients living with ARDs.

Clinical questions and SLR

The Restricted Task Force worked to determine the PICO (Population, Intervention, Comparison, Outcome) questions related to the exposure of antiviral therapies and antibody products anti-

SARS-CoV-2 in immunocompromised ARD patients (with a particular focus on CTDs patients) affected by COVID-19. Considering the particularity of the topic and in order to increase the likelihood of finding relevant and useful data on antiviral drugs and antibody products for treating COVID-19 to be potentially generalised, the population was identified as not only constituted by patients with ARDs but immunocompromised patients in general (*e.g.* haematologic, oncologic patients). Thus, the specific clinical questions for the SLR were the following:

i) What is the evidence for the benefits and harms of anti-SARS-CoV-2 antiviral therapies in treating immunocompromised patients affected by COVID-19?
ii) What is the evidence for any benefits and harms related to treatment with anti-SARS-CoV-2 antibody products in immunocompromised patients affected by COVID-19?

The SLR on the specific clinical questions was performed by the four research fellows (GAR, SB, CC, PT) under the supervision of the methodologist (RT). The literature search was conducted using PubMed and Embase database, searching for relevant papers through October 2022; papers were selected, critically appraised and summarised according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14). To better contextualise the available data according to the different phases of the pandemic, an arbitrary temporal classification of the analysed studies was defined (Table I). Details on the literature search strategy are included in the supplementary material.

Consensus finding

A first draft including OP and PtC statements was prepared and discussed during the Extended Task Force meeting. After the meeting, the edited draft was distributed to the Extended Task Force members via EU survey (15), asking to indicate their agreement with each statement with "yes" or "no" and to vote on their level of agreement (LoA), using a scale of 0–10 (0 indicating no agreement at all and 10 indicating full agreement). A consensus is accepted if >75% (threshold pre-agreed) of the members voted in favour of each statement. The mean and SD of the LoA, as well as the percentage of the Task Force members with an agreement ≥8 were reported. The Level of Evidence (LoE) and the Strength of the Recommendations (SoR) were assigned according to the Oxford 2011 Levels of Evidence (16).

Table I. Arbitrary temporal segmentation of the pandemic.

Phase number	Definition
I	Alpha to delta variants and no vaccines
II	Delta variant; vaccination ongoing
III	Rise of omicron variant, primary vaccination cycle likely complete
IV	Emergence of new omicron subvariants, booster vaccination ongoing

Results

The exceptionality of the new emerging topic and the consequent scarcity of high-quality evidence required the creation of PtC rather than recommendations. SLR results are summarised described in the supplemental material; in brief, 615 papers were reviewed, and 26 studies were selected for inclusion. The use of evidence was done in a hierarchical manner, *i.e.* using those on ARDs patients as the first option, mixed populations as the second option in the absence of sufficient data on RMD patients only, and lastly data on immunocompromised non-RMD patients. Overall, the quality of evidence was poor, as the sample size was frequently low, and the majority of studies were descriptive without a comparator group. Moreover, the studies were characterised by a significant heterogeneity, in terms of the study timeframe (*e.g.* available drugs, circulating SARS-CoV-2 variants, vaccination status of the target population) and of additional treatments (corticosteroids, heparin, other drugs). The LoE ranged from 4 to 5, due to the scarcity of high-level evidence. Despite the paucity of data, the information was nonetheless relevant and allowed to draft the PtC. The discussion on the data available and the expert opinion produced 6 PTC. Moreover, after the discussion of the results of the SLR, the Extended Task Force agreed on a final set of 3 OP and 6 PtC, that are summarised in Table II. The LoA was globally high, ranging from 8.7 to 9.7.

Overarching principles

The Task Force formulated the following OP in order to reinforce the necessity to adhere to some general principles linked to the infection itself and to the major preventive measures for COVID-19 in patients with ARDs.

(A) *Patients with ARDs on immunosuppressive treatments may be susceptible to being infected for a prolonged period and this may have an impact on the therapeutical management of their underlying disease* [LoA: 9.1 (1.3)].

Prolonged shedding of SARS-CoV-2 has been reported in immunocompromised patients (17); people with ARDs may be susceptible to prolonged COVID-19 symptoms, and this can be due to different reasons, such as longer duration of viral infection, a disturbed immunity and the use of immunosuppressive medications (18). In this regard, the COVID-19 Global Rheumatology Alliance (GRA) investigated the duration of COVID-19 symptoms among people with ARDs, observing that about 1 out of 4 patients experienced prolonged COVID-19 symptom duration (defined as lasting 28 days or longer) and even 1 out of 10 experienced symptoms lasting over 90 days (11). Therefore, this principle is mainly aimed to raise awareness on the potential risk that a prolonged infection may have on ARDs patients, especially in the management of the immunosuppressive drugs and in spreading the infection itself. This overarching principle was accepted in the first round of the voting process (98% agreed, first round, n=46).

(B) *COVID-19 vaccination is one of the main measures to prevent severe disease for patients with ARDs.*

The number and intervals of additional

Table II. ERN ReCONNET points to consider for treating ARDs patients with antiviral therapies and antibody products anti-SARS-CoV-2.

	Overarching principles	LoE	SoR	LoA mean (SD)	≥8/10 (%)
A	Patients with ARDs on immunosuppressive treatments may be susceptible to being infected for a prolonged period and this may have an impact on the therapeutical management of their underlying disease.	**N/A**	**N/A**	**9.1 (1.3)**	**89**
B	COVID-19 vaccination is one of the main measures to prevent severe disease for patients with ARDs. The number and intervals of additional (booster) vaccinations may differ among countries, depending on the epidemiological situations.	**N/A**	**N/A**	**9.3 (1.2)**	**89**
C	The therapeutic management of ARDs patients with COVID-19 needs a periodic update on emerging epidemiological, virological and pharmacological data.	**N/A**	**N/A**	**9.7 (0.7)**	**98**
	PtC	**LoE**	**SoR**	**LoA mean (SD)**	**≥8/10 (%)**
1	Pre-exposure prophylactic treatment can be considered in ARDs patients who are at risk of severe COVID-19.	**4**	**C**	**8.7 (1.7)**	**82**
2	To date, there is no sufficient evidence to recommend the use of SARS-CoV-2 antibody serologic testing to guide the clinical decision about the administration of anti-SARS-CoV-2 monoclonal antibodies as pre-exposure prophylaxis in ARDs.	**5**	**D**	**8.9 (1.5)**	**89**
3	Treatment with antiviral drugs may be considered in immunocompromised ARDs patients with mild to moderate COVID-19; a multidisciplinary approach is crucial to ensure the proper treatment decision and timing.	**4**	**C**	**9.2 (1.2)**	**87**
4	Treatment with anti-SARS-CoV-2 monoclonal antibodies can be considered in immunocompromised ARDs patients with mild to moderate COVID-19.	**4**	**C**	**8.7 (1.8)**	**86**
5	Treatment with antivirals alone or in combination with monoclonal antibodies can be considered in immunocompromised ARDs patients with mild to moderate COVID-19, provided that available drugs are compatible with the virological characteristics of newly emerging SARS-CoV-2 variants and taking into account possible interactions with concomitant therapy.	**4**	**C**	**8.9 (1.9)**	**84**
6	There is no sufficient evidence to recommend the use of high-titre COVID-19 convalescent plasma in ARDs patients with COVID-19 who are taking immunosuppressive drugs	**5**	**D**	**9.2 (1.3)**	**91**

PtC: points to consider; LoE: level of evidence; SoR: strength of recommendations; LoA: level of agreement. SD: standard deviation.

(booster) vaccinations may differ between countries depending on the epidemiological situations
[LoA: 9.3 (1.2)].

The Task Force strongly emphasised that vaccination is the most effective way to reduce the risk of COVID-19 related hospitalisation, severe disease, and death as well as to protect health systems (19-21). The epidemiological situations, in different countries, may have an impact on the number and intervals of additional (booster) vaccinations recommended. The Task Force unanimously agreed on this principle (100% agreed, first round, n=46).

(C) *The therapeutic management of ARDs patients with COVID-19 needs a periodic update on emerging epidemiological, virological, and pharmacological data* [LoA: 9.7 (0.7)].

The management of COVID-19 in people with ARDs should be tailored based on the risk factors for poor prognosis, which includes older age, type of immunosuppressive therapies, presence of comorbidities, disease activity of the underlying rheumatic condition and the clinical severity of COVID-19 (18, 22-23). Therefore, this principle is aimed at highlighting how important is to encourage and provide periodic updates on the therapeutic management of ARDs patients with COVID-19 considering also the epidemiological and virological situation (*i.e.* the emergence of new variants of the virus), as well as new pharmacological data (*i.e.* availability of new drugs, potential drugs interactions). The Task Force unanimously agreed on this principle (100% agreed, first round, n= 6).

Points to consider

1. *Pre-exposure prophylactic treatment can be considered in ARDs patients who are at risk of severe COVID-19* [LoE: 4, SoR: C, LoA: 8.7 (1.7)].

In severely immunocompromised patients, vaccination may not generate an adequate immune response, and they may be still vulnerable to severe SARS-CoV-2 infection (17). Pre-exposure prophylaxis gives additional immunity to help prevent COVID-19 and can be administered to people who are moderately or severely immunocompromised due to a medical condition or immunosuppressive treatment (19).
During the pandemic evidence emerged regarding the safety and efficacy of pre-exposure prophylaxis in ARDs patients, although only from single-centres cohort studies (24-30), which are summarised in Tables III and IV. Significant real-world experience was identified from a literature review by Calabrese *et al*. describing outcomes of COVID-19 in patients with immune-mediated inflammatory diseases (IMIDs) treated with B cell depleting therapies (BCDTs) or with inborn errors of humoral immunity (IEI) (24); 412 of IMIDs and IEI patients received tixagevimab/cilgavimab as pre-exposure prophylaxis and, notably, among these only 12 breakthrough infections were reported, with mild disease in 11 and only one patient experienced severe (non-fatal) disease. Thus, even if the study was limited by the lack of a comparator group and potential bias (also due to the Omicron epoch) the data are really encouraging. Similar data in terms of low percentage of COVID-19 disease was reported by Oraya *et al*. who described 674 immunocompromised patients (less than one fourth affected by ARDs) who received tixagevimab/cilgavimab during a preexposure prophylaxis program; among these, only 1.2% of the patients were subsequently diagnosed with SARS-CoV-2 infection (25) and no deaths were reported. The Task Force, therefore, emphasised that on the basis of the available data, pre-exposure prophylactic treatment can be considered in ARDs patients, especially in those who are at high risk of severe COVID-19, such as the case of the initiation of high-dose glucocorticoids or B cell-depleting therapies. This PtC was accepted in the first round of the voting process (94% agreed, first round, n= 46).

2. *To date, there is no sufficient evidence to recommend the use of SARS-CoV-2 antibody serologic testing to guide the clinical decision about the administration of anti-SARS-CoV-2 monoclonal antibodies as pre-exposure prophylaxis in ARDs*
[LoE: 5, SoR: D, LoA: 8.9 (1.5)].
Since insufficient data were found on the use of SARS-CoV-2 antibody serologic testing to guide the clinical decision to administer anti-SARS-CoV-2 monoclonal antibodies as pre-exposure prophylaxis, the Task Force agreed not to provide specific recommendations about it.
This PtC was accepted in the first round of the voting process (98% agreed, first round, n=44).

3. *Treatment with antiviral drugs may be considered in immunocompromised ARDs patients with mild to moderate COVID-19; a multidisciplinary approach is crucial to ensure the proper treatment decision and timing*
[LoE: 4, SoR: C, LoA: 9.2 (1.2)].
Literature data have shown that antiviral drugs have been also used in immunocompromised patients, usually at the doses and durations as recommended for the general population. Although the evidence is not strong and data collected are heterogeneous even regarding the different periods of the pandemic (*i.e*., alpha to delta variants and no vaccines; delta variant, vaccination ongoing; rise of omicron variant, primary vaccination cycle likely complete; emergence of new omicron subvariants, booster vaccination ongoing; summarised in Table I), globally, the data on safety and efficacy are encouraging (29, 31-46) (summarised in Tables III and IV). For this reason, the rationale for this PtC is to emphasise that having an ARD does not contraindicate the use of antiviral drugs and that they may be considered in case of mild to moderate COVID-19. We defined mild COVID-19 disease as the presence of one or more signs and symptoms (*e.g*. fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, loss of taste and smell) in absence of shortness of breath, dyspnoea, or abnormal chest imaging and moderate COVID-19 disease: the presence of lower respiratory disease, with SpO2 ≥94% on room air.
This PtC was unanimously accepted in the first round of the voting process (100% agreed, first round, n=45).

4. *Treatment with anti-SARS-CoV-2 monoclonal antibodies can be considered in immunocompromised ARDs patients with mild to moderate COVID-19*
[LoE: 4, SoR: C, LoA: 8.7 (1.8)].
The evidence on the use of anti-SARS-CoV-2 monoclonal antibodies in immunocompromised ARDs patients was limited, however the data (Tables III and IV) have globally shown a good safety profile with the use of monoclonal antibodies in immunocompromised patients, including those with ARDs (25, 27, 29, 32, 39, 41, 42, 43, 47-49).
As for PtC no. 3, this PtC aims to emphasise that anti-SARS-CoV-2 monoclonal antibodies can also be considered in immunocompromised ARDs patients with mild to moderate COVID-19, while highlighting that having an ARDs does not contraindicate their use.
This PtC was accepted in the first round of the voting process (96% agreed, first round, n=44).

5. *Treatment with antivirals alone or in combination with anti-SARS-CoV-2 monoclonal antibodies can be considered in immunocompromised ARDs patients with mild to moderate COVID-19, provided that available drugs are compatible with the virological characteristics of newly emerging SARS-CoV-2 variants and taking into account possible interactions with concomitant therapy*
[LoE: 4, SoR: C, LoA: 8.9 (1.9)].
This PtC is linked with PtC no. 3 and no. 4 and is aimed not only to reinforce that both antivirals and monoclonal antibodies should (?) be considered (alone or in combination) (24-49) when treating patients with ARDs, but also to highlight that the approach to COVID-19 in ARDs should always be contextualised to in the dynamic epidemiological scenario of possible newly emerging SARS-CoV-2 variants, always taking into account possible interactions with concomitant therapy for the underlying disease and/or comorbidities. This PtC was accepted in the first round of the voting process (95% agreed, first round, n=44).

Table III. Number of patients by study, type of intervention and drug among the identified studies.

	Total patients	**Studies**	Ahluwalia *et al.*,2020	Destras *et al.*,2021	Calabrese, Kirchner, Husni, *et al.*,2022	Ordaya *et al.*,2022	D'Abramo *et al.*,2022	Shahram *et al.*,2022	Naghashzadeh *et al.*,2021	Zhu *et al.*,2020	Calvo *et al.*,2021	Bermas *et al.*,2022	Furlan *et al.*,2021	Fagni *et al.*,2022	Bronstein *et al.*,2022	Sun *et al.*,2022	Taha *et al.*,2021	Ocon *et al.*,2022	Ferre *et al.*,2021	Bruel *et al.*,2022	Weinbergerova *et al.*,2021	Lafont *et al.*,2022	Brown *et al.*,2022	Franchin *et al.*,2021	van Laarhoven *et al.*,2021	Fragoulis *et al.*,2022	Conte *et al.*,2022	Calabrese, Kirchner, V	illa-Forte, *et al.*,2022
Total numbers	1494	26	2	2	21	674	21	11	11	10	3	2	4	22	2	35	2	43	3	29	32	67	28	4	5	31	18	412
Children	3	1	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Treatments for COVID-19	368	22	2	2	21	9	21	11	11	10	3	2	4	0	2	35	2	0	3	3	32	42	28	4	5	31	0	0
Antivirals	206	17	2	0	0	0	21	11	9	10	3	2	4	0	1	35	2	0	1	0	32	16	21	0	5	31	0	0
REM	115	12	2	0	0	0	21	4	9	0	2	0	4	0	1	0	2	0	1	0	32	16	21	0	0	0	0	0
NIR/RIT	64	2	0	0	0	0	0	0	0	0	0	0	0	0	0	35	0	0	0	0	0	0	0	0	0	29	0	0
MOL	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0
LOP/RIT	4	3	0	0	0	0	0	1	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Others	22	3	0	0	0	0	0	7	0	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0
Monoclonal antibodies	96	11	0	2	21	9	17	0	0	0	0	0	0	0	1	0	2	0	2	3	0	26	9	4	0	0	0	0
BAM/ETE	8	5	0	2	0	0	1	0	0	0	0	0	0	0	1	0	0	0	2	0	0	0	0	2	0	0	0	0
SOT	19	3	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	12	0	0	0	0	0	0
CAS/IMD	51	6	0	0	21	0	16	0	0	0	0	0	0	0	0	0	0	2	0	0	0	1	9	2	0	0	0	0
TIX/CIL	9	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	0	0	0	0	0	0
BEB	5	1	0	0	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unspecified/Others	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0
Polyclonal antibodies	66	9	0	0	0	0	7	0	2	7	0	0	4	0	2	0	0	0	0	0	32	1	6	0	5	0	0	0
CP	56	7	0	0	0	0	7	0	0	0	0	0	4	0	1	0	0	0	0	0	32	1	6	0	5	0	0	0
IVIG	10	3	0	0	0	0	0	0	2	7	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Prophylaxis for COVID-19	1213	7	0	0	0	674	0	0	0	0	0	0	0	22	0	0	0	43	0	29	0	15	0	0	0	0	18	412
Monoclonal antibodies	1213	7	0	0	0	674	0	0	0	0	0	0	0	22	0	0	0	43	0	29	0	15	0	0	0	0	18	412
TIX/CIL	1191	6	0	0	0	674	0	0	0	0	0	0	0	0	0	0	0	43	0	29	0	15	0		0	0	18	412
CAS/IMD	40	2	0	0	0	0	0	0	0	0	0	0	0	22	0	0	0	0	0	18	0	0	0		0	0	0	0

BAM: bamlanivimab; BAM/ETE:bamlanivimab + etesivimab; BEB:bebtelovimab; CAS/IMD: casirivimab + imdevimab; CIL: cilgavimab; CP: convalescent plasma; ETE: etesivimab; IFNγ: interferon gamma; IMD: imdevimab; IVIG: intravenous (polyclonal) immunoglobulins; LOP: lopinavir; LOP/RIT: lopinavir + ritonavir; MOL: molnupiravir; NIR: nirmatrelvir; NIR/RIT:Nirmatrelvir + ritonavir (Paxlovid ®); REM: remdesivir; RIT: ritonavir; SOT: sotrovimab; TIX: tixagevimab; TIX/CIL: tixagevimab + cilgavimab (Evusheld ®).

Table IV. Prophylaxes and treatments for COVID-19 in immunocompromised subjects.

Reference	Phase	Study design	Sample size						Interv-ention	Immunosuppressants	Comparison	Drugs	Endpoint	Safety outcomes	Efficacy outcomes
			G	D	T	CTD	RMD	I							
Ahluwalia *et al*., 2020	I	MCS	358	5	2	0	0	5	T AZA	MMF, TAC, CyA,	None	REM	ND	ND without REM	Of 5/358 patients with COVID-19, 2/2 received REM and survived, 2/3 survived
Destras *et al*., 2021	II	TCS	2	2	2	0	0	2	T	ND	None	BAM	ND	ND	1/2 died, the other patient had respiratory failure; escape variants->virological response failure
Calabrese, Kirchner, Husni, *et al*., 2022	II	SCO	1677	74	21	5	29	0	T	AZA, MTX, MMF, BCDT	mAb vs. no mAb	CAS/IMD	C,S,Se	ND	1/21 hospitalized and 0/21 dead with mAb vs 23/53 hospitalized and 6/53 dead without mAb (p=0.006)
Ordaya *et al*., 2022	III	SCO	674	674	P 674 T 4+5	ND	155	519	P, T	AZA, TAX, CT, BCDT, CyA, MMF	None	TIX/CIL SOT, BEB	C, Se	ND	8/674 had COVID-19 (none RMD) within 2 months->4/8 SOT: none severe COVID-19. Additional 6/674 (initially not reported) had COVID-19->5/6 BEB: none
D'Abramo *et al*., 2022	II	SCO	21	21	21	0	4	21	T	BCDT, CT	mAb vs. CP	REM, CAS/IMD, BAM, CP	S, V	ND	21/21 REM, 16/21 CAS/IMD, 3/21 BAM; 7/21 CP; 1/21 died and had received no mAb; decreasing trends of length of stay and time to virological response
Shahram *et al*., 2022	I	SCO	61	11	11	0	11	0	T	AZA, MTX, CYC, aTNF, IFNα	Hosp. vs. non Hosp	Antivirals	ND	ND	Antivirals (multiple) were associated to hospitalisation
Naghashzadeh *et al*., 2021	I	SCS	13	13	≥9	0	0	13	T	Tacrolimus, MMF, CyA	None	REM, IVIG	S	ND	9/13 REM, 2/13 IVIG; 12/13 survived; 1/13 died for respiratory and renal failure.
Zhu *et al*., 2020	I	SCO	10	10	10	0	0	10	T	TAC, MMF, CyA, other	None	Antivirals, IVIG	S	No organ	10/10 antivirals, 7/10 IVIG. 9/10 survived
Calvo *et al*., 2021	I	SCS	8	8	3	2	8	8	T	TAC, MMF, CYA, IVIG, AZA	None	REM, LOP/RIT	S	ND	1 REM->died (baseline severe anti-MDA5 JDM with ILD), 2 LOP/RIT survived
Bermas *et al*., 2022	I	MR	39	39	2	15	39	ND	T	ND	None	LOP/RIT	ND	ND	ND (all patients in the cohort survived)
Furlan *et al*.,2021	I	SCS	4	4	4	0	0	4	T	BCDT	None	REM, CP	S, V	ND	4/4 survived and had virological response
Fagni *et al*., 2022	II	SCO	22	22	22	3	22	22	P	BCDT	None	CAS/IMD	ND	No side effects reported	1/5 with COVID.19 exposure had COVID-19
Bronstein *et al*., 2022	I	TCS	2	2	2	0	0	2	T	CT, BCDT	None	BAM, REM, CP	V	ND	Failure to induce virological response
Sun *et al*., 2022	II	SCO	114	114	114	ND	7	35	T	ND	Early vs. late NIM/RIT	NIR/RIT	V	ND	Shorter viral clearance with early NIR/RIT
Taha *et al*., 2021	I	TCS	2	2	2	0	0	2	T	NA	None	CAS/IMD, REM	S, V	ND	Both patients survived and cleared the virus
Ocon *et al*.,2022	III	SCS	43	43	43	5	43	43	P	COR, MTX, AZA, LFN, SSZ, MMF, AVA	Cohort vs. general pop.	TIX/CIL	C	Excellent safety profile	COVID-19 incidence rate 2.2% within 100 ± 33 days vs 4.3% in the general population within 121 days
Ferre *et al*., 2021	I	TCS	2	2	2	0	0	2	T	None	None	BAM/ETE, REM	ND	No adverse events	2/2 BAM/ETE, 1/2 REM. Both patients survived and developed
Bruel *et al*., 2022	III	MCO	29	29	29	1	26	29	P, (T)	BCDT	None	(CAS/IMD), TIX/CIL, (SOT)	C	ND	4/29 COVID-19, 1 severe; 3/4 SOT->outcome unknown. Additional *in vitro* data showing non-efficacy of most mAb
Weinbergerova *et al*., 2021	II	SCO	32	32	32	0	0	32	T	ND	None	REM, CP	S, Se	No significant adverse events	3/32 died, 20/32 severe or critical COVID-19
Lafont *et al*., 2022	III	SCO	67	67	P 15 T 42+6	ND	ND	67	P, T	CYC, MMF, COR, CT, BCDT, CyA, EVE, BELA	P vs. T vs. no intervention	TIX/CIL, REM, SOT, CAS/IMD, CP	S	No adverse events	15/67 prophylaxis: 0/15 died vs 2/52 without prophylaxis ǀ 42+6/67 treated with mAb and/or antivirals: all survived ǀ 10/67 no prophylaxis and no treatment: 2/10 died
Brown *et al*., 2022	II	SCO	31	31	28	0	0	31	T	BCDT	Combination vs. monotherapy	REM, CAS/IMD, CP	V	ND	13/14 combination vs 7/14 monotherapy cleared the virus. In recurrent episodes, treatment more effective than no treatment
Franchin *et al*., 2021	II	SCS	4	4	4	2	3	2	T	MMF, aIL17	None	BAM, CAS/IMD	S, Se	No adverse events	2/4 BAM, 2/4 CAS/IM: 4/4 uneventful COVID-19 (mild at presentation)
van Laarhoven *et al*., 2021	I	SCS	5	5	5	0	0	5	T	MMF, TAC, BCDT, ALE	None	IFNγ, CP	S, Se	graft rejection (n=1/5)	5/5 IFNγ, 4/5 CP: 1/5 died, 4/5 survived and were extubated
Fragoulis *et al*., 2022	IV	SCO	31	31	31	10	31	31	T	COR, DMARDS	None	NIR/RIT, MOL	S	3/31 mild adverse events	0/31 dead or hospitalised, 2/31 relapses
Conte *et al*., 2022	IV	SCO	18	18	18	0	0	18	P	BCDT	None	TIX/CIL	ND	ND	100% serological response, no clinical data
Calabrese, Kirchner, Villa-Forte, *et al*., 2022	III	SCO	412	12 T ND	P 412	2	12	12	P	BCDT	None	TIX/CIL	C, Se	1/12 ITP flare	12/412 had COVID-19 (unknown timeframe); 11/12 low NIH score (1/12 hospitalised)

SCS: single-centre case series; SCO: single-centre cohort study; TCS: two-patient case series; MCO: multicentre cohort study; MCS: multicentre case-series MR: multicentre registry; G: global size; D: described subjects; CTD: patients with connective tissue diseases; I: immunocompromised subjects; RMD: patients with rheumatic musculoskeletal diseases; T: treated subjects; P: prophylaxis; T: treatment; aIL17: anti-IL17; ALE: alemtuzumab; aTNF: anti-TNF; AZA: azathioprine; BCDT: B-cell depleting therapy; BELA: belatacept; COR: corticosteroids; CT: chemotherapy; CYA: cyclosporine A; CYC: cyclophosphamide; DMARDs: (unspecified) disease modifying anti-rheumatic drugs; EVE: everolimus; IFNα: interferon alpha; LFN: leflunomide; MMF: mycophenolate mofetil (or analogues); MTX: methotrexate; SSZ: sulfasalazine; TAC: tacrolimus; REM: remdesivir; ND: no data; S: survival; Se: COVID-19 severity; C: COVID-19; V: virological clearance.

6. *There is no sufficient evidence to recommend the use of high-titre COVID-19 convalescent plasma in ARDs patients with COVID-19 who are taking immunosuppressive drugs*
[LoE: 5, SoR: D, LoA: 9.2 (1.3)].
As insufficient data were found on the efficacy and safety of high-titre COVID-19 convalescent plasma in ARDs patients with COVID-19, the Task Force agreed on not providing a recommendation on their use.
This PtC was unanimously accepted in the first round of the voting process (100% agreed, first round, n=44).

Discussion

Here we report the ERN ReCONNET OP and PtC for treating ARDs patients with anti-SARS-CoV-2 antiviral therapies and antibody products. The work was developed in the framework of the ERN ReCONNET using an evidence-based and expert opinion-based approach, involving a significant part of the network members, including patients' advocates. The PtC have the main scope to serve as reference for all the stakeholders involved in the care process of ARDs patients affected by COVID-19, in order to make the management of the infection more homogenous across different countries and centres.
As also stated in the overarching principles, patients with ARDs on immunosuppressive treatments may be susceptible to be infected for a prolonged period and this may have an individual and epidemiological impact. Indeed, patients may have to suspend the immunosuppressive drugs in the context of a prolonged infection, and this may have a direct impact on disease activity and prognosis. On the other hand, a prolonged infection increases the risk of spreading the virus and foster new variants (10, 19). Clinicians have to be aware of these risks in order to manage ARDs patients affected by COVID-19 in the most appropriate way.
Since the beginning of the COVID-19 pandemic, different therapies have been used in order to minimise the risks of poor outcome in immunocompromised patients including individuals affected by ARDs (50, 51). Besides the few trials available, the real-life experience on the use of antiviral drugs and antibody products continues to grow gradually. COVID-19 vaccination is the main strategy to prevent severe disease in ARDs patients; beside this, a substantial number of these patients have been treated with antiviral drugs or monoclonal antibodies. However, in absence of specific guidelines ARDs patients from different countries (and frequently also in the same country/region) may not be treated with a homogenous approach. As this is a clinical and patients' relevant unmet need (52), we defined pragmatic PtC, based on scarce and limited quality evidence and on expert opinion of clinicians, with the contribution of patients' advocates.
One of the main messages is that pre-exposure prophylactic treatment can be considered in ARDs patients who are at risk of severe COVID-19, even if there is no sufficient evidence to recommend the use of SARS-CoV-2 antibody serologic testing to guide the clinical decision about their administration. Encouraging data in terms of safety and efficacy derived from different (albeit few) single cohort studies on the use of antiviral drugs or monoclonal antibodies. Therefore, it is important to highlight that booster and pre-exposure treatment can be considered as complementary, as well as the need to early use antiviral agents and ant- SARS-CoV-2 antibody products in most fragile patients. However, the therapeutic management of ARDs patients with COVID-19 needs an accurate balance of different dimensions, including the epidemiological and virological up to date for contextualising the treatment approach, especially regarding the risk of newly emerging SARS-CoV-2 variants. New pharmacological evidence and drug availability might further optimise the management, but possible drug interactions with concomitant therapy always need to be taken into considerations.
In conclusion, these ERN ReCONNET PtC are intended to facilitate a more harmonised approach to the care of individuals with ARDs affected by COVID-19.

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Competing interests

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