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Review Article

Practical Recommendations for the Management of Patients with ITP During the COVID-19 Pandemic

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Abstract. The current COVID-19 pandemic requires revisiting our current approach to major blood disorders, including ITP (Immune Thrombocytopenia), stirring up the production of several disease-specific practical guidelines. This report describes an updated version of consensus-based practical guidelines on the management of ITP, adapted to the Italian health system and social context. It highlights the role of the hematologist in offering guidance for choosing differentiated approaches in relation to specific circumstances and is intended to provide them with a useful tool for sharing the decision-making process with their patients.

Probably, the greatest risk to avoid for a patient with suspected, ongoing or relapsed ITP - that is not severe enough to place him or her at risk for major bleeding - is to be infected in non-hospital and hospital healthcare settings. This risk must be carefully considered when adapting the diagnostic and therapeutic approach.

More in detail, the document first addresses the appropriate management for COVID-19 negative patients with newly diagnosed ITP or who experience a relapse of previous ITP, according to first and second lines of treatment and then the management of COVID-19 positive patients according to their severity, from paucisymptomatic to those requiring admission to Intensive Cure Units (ICU). The pros and cons of the different treatments required to correct platelet count are discussed, as are some specific situations, including chronic ITP, splenectomy, thromboembolic complication and anti COVID-19 vaccination.

Keywords: ITP; Immune thrombocytopenia; COVID-19; Practical recommendations.

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Introduction. The current COVID-19 emergency, which is still in full development, suggests to keep ITP management guidelines updated - giving them a wide dissemination. For Italy, this has been done thanks to the collaboration of many interested stakeholders (HPF, GIMEMA, SISET, Ematologia in Progress, AIPIT). A first version, available on request, released in June 2020 by the Hematology Project Foundation (HPF), was made available to several ITP centers as well as to individual patients.

This update was coordinated by Nicola Vianelli in collaboration with FPE with the aim of adapting some of the previous practical recommendations to the new knowledge and to the suggestions collected in some recent discussion forums organized by FPE. Moreover, the panel of experts was enlarged and preliminary results from a recent survey on the management of patients with ITP during this pandemic, jointly conducted by HPF and GIMEMA with the involvement of all major Italian referral centers for ITP, have been taken into consideration in this update. We reiterate the strictly indicative value of the recommendations due to their limited scientific evidence and the consequent low level of recommendation compared to the so-called "trustworthy guidelines".[1,2] Within these limitations, we intend to offer guidance to physicians who treat ITP patients while providing them with a useful tool for sharing the decision-making process with the patients.

Furthermore, after the release of the first version of the document, additional discussion forums, promoted by HPF, were held among experts from the major Italian ITP centers, and the recommendations of English colleagues[3] and an updated version of the FAQs by ASH[4] were taken in due account.

The term COVID-19 defines the disease caused by the novel coronavirus, named SARS-CoV-2. For convenience we will use the term COVID-19 extensively to refer to the disease and infected patients, using the term SARS-CoV-2 where required by the context.

Thrombocytopenia and COVID-19.

Generalities. Thrombocytopenia - defined as a platelet count < 150,000/μL - is quite frequent in patients with COVID-19, reaching up to 36% of cases,[5] whereas cases with moderate or severe thrombocytopenia are quite rare. However, within an analysis of 183 patients who were hospitalized for COVID-19, thrombocytopenia < 100,000/μL (7 cases) and < 50,000/μL (5 cases) was observed in the 21 patients who died[6] confirming an association between the level of thrombocytopenia and the severity of the clinical picture of SARS-CoV-2 infection.[6,7] According to a recent revision, patients with severe thrombocytopenia hospitalized for COVID-19 (values < 50,000/μL) have a mortality relative risk 13.7 times higher compared to patients with a normal platelet count.[8] COVID-19 thrombocytopenia is generally concurrent with a complex coagulopathy characterized by APTT/PT prolongation and also by a marked increase of D-dimer while fibrinogen is either within normal ranges or notably increased. This coagulopathy (DIC-like) first represents a local pulmonary vascular reaction and then a systemic reaction to the hyper inflammation and cytokine storm triggered by the viral infection. The virus interferes directly with the coagulation system or acts indirectly through the immune response.[9-11] This results in a prothrombotic state with probable activation of endothelium and platelets.[12] Similar phenomena are observed in other serious infections (septicemia, SARS, MERS) that require treatment in the Intensive Care Unit (ICU). Among the many factors responsible for thrombocytopenia, exposure to numerous drugs, hemodialysis and ECMO (extra Corporeal Membrane Oxygenation) should also be noted. No cases of heparin-induced thrombocytopenia (HIT) have been reported so far, which only exceptionally occurs with the low molecular weight heparin (LMWH) commonly used in Italy, but less infrequently with the use of standard heparin. However, this eventuality should be considered in differential diagnoses.

Role of the hematologist. Based on the experience of the authors of these recommendations, Italian internists and anesthesiologists treating COVID-19 patients require hematologic consultation almost exclusively in patients in whom the suspicion of ITP appears likely, such as in case of a rapid (1-3 days) onset of severe thrombocytopenia with levels < 30-50,000/μL. In these cases, the consultation of a hematologist, preferably an expert in hemostasis and thrombosis, can be crucial in excluding other causes of thrombocytopenia, such as HIT (which is very rare with the use of LMWH), drug-induced thrombocytopenia, bone marrow aplasia/megakaryocytic aplasia, thrombotic thrombocytopenic purpura. The hematologist may also be consulted in the interpretation of coagulopathy and in the choice of a prophylactic or therapeutic approach to thromboembolic phenomena (see paragraph *"Management of second or further line"*).

At the moment, there is no evidence of an increased incidence of ITP in patients with COVID-19 infection. However, at least 30 cases of severe thrombocytopenia classifiable as COVID-19-associated with reduced response to corticosteroids and immunoglobulins have been reported (individual publication references are

available upon request). This apparent low incidence of ITP in patients with COVID-19 will, however, need to be confirmed by literature data, as it is well known that some viral infections may be a factor favoring the onset of ITP.

Management of COVID-19 Negative Patients with Newly Diagnosed ITP or who Experience a Relapse of Previous ITP.

Preface. This section refers to patients who are COVID-19 negative on the basis of molecular swab testing or antigen testing, or to asymptomatic patients with an unavailable result at the time of initiation of therapy.

Probably the greatest risk for a patient with suspected ITP or relapse of previous ITP that is not severe enough to place him or her at risk for major bleeding, is to be infected in non-hospital and hospital healthcare settings, through contact with contaminated objects, or directly by health care personnel, especially if personnel and patients are not adequately equipped with prescribed personal protective equipment. This risk must be carefully considered when adapting the diagnostic and therapeutic approach that is proposed to the patient.

However, in the suspicion of a new diagnosis or of a relapse of ITP, we suggest to perform appropriate tests to ascertain the absence of previous or ongoing SARS-CoV-2 infection, if these are available and if they can be performed without any predictable risk of infection. Molecular testing by nasopharyngeal or oropharyngeal swab using the RT-Real Time PCR technique remains the standard test. If not possible or in case a quick response is required, a rapid antigenic test can be considered, remembering however that the sensitivity of this type of test can be just above or equal to 70% of positive cases (up to 30% of positive cases not identified). Serologic testing has a minimal role and might be reserved for asymptomatic patients, to rule out prior or early COVID-19 disease. In addition, serologic testing has limitations, for example in patients treated in recent months with rituximab, because of insufficient antibody response, and generally positivity appears about 12 days after the infection, making these tests of little use for the diagnosis of recent infection. Moreover, it has not been established whether the presence of the so-called neutralizing or protective antibodies prevents the patient from being re-infected by SARS-CoV-2. See also the ISS website.[13]

Asymptomatic patients with an unavailable result at the time of initiating therapy are considered from a practical standpoint to be COVID-19 negative.

Moreover, always in the light of the risks of contagion, we should consider that - except for particular situations (advanced age, previous history of major bleeding) - most patients do not present relevant bleeding symptoms in the presence of platelet counts ≥ 10-20,000/μL. Therefore, in stable patients, even if with low platelet counts, as long as they have no bleeding symptoms, it is recommended to reduce the frequency of ambulatory visits and platelet count checks to reduce the risk of contagion associated with patients' access to health care facilities..

First-line treatment. First-line treatment of ITP in COVID-19-negative patients does not require substantial changes from recent international guidelines.[14,15] There is no evidence that corticosteroid use increases the risk of developing COVID-19 infection or of worsening its course.[16]

Therefore, the initial treatment remains that based on corticosteroids, such as prednisone 1 mg/kg/day (maximum initial dose 80 mg) for 3-4 weeks including the tapering phase. The current practice in some centers to use dexamethasone (40 mg/day for 4 days with several cycles repeated at intervals of 10 days up to a maximum of 4 cycles), is not supported by the indications on ITP and COVID-19 produced by British colleagues[3] and by the updated version of the FAQs by ASH[4] and therefore could be reserved for cases with a very low platelet count (< 10,000/μL), especially if with hemorrhagic symptoms, in which a very rapid increase in platelet count is considered clinically relevant. However, in such cases - if applicable - the administration of intravenous immunoglobulins (IVIg), 400 mg/day for 5 days or 1 g/kg/day for 1-2 days, is preferred. In case of major life-threatening bleeding or associated with severe organ damage, such as cerebral hemorrhage,[17] the use of platelet transfusion remains recommended. There are no reported cases of SARS-CoV-2 transmission through platelet transfusions.

However, it is reasonable to try to avoid or to limit steroid use in a severe pandemic situation (see paragraph "*Patients admitted into ICU"* for the use of corticosteroids in symptomatic COVID-19 patients). Therefore, in the absence of need for a rapid increase of platelet count, the early (off label) use of a TPO-RA (possibly combined with IVIg) is suggested, aware that its possible efficacy will require 1-2 weeks to become apparent and considering that dose adjustments could be made on the basis of telephone or electronic (email) contacts, with platelet counts performed in laboratories located close to the patients. This is the only approach feasible in patients with significant contraindications to steroids. The use of tranexamic acid (about 15 mg/kg/day every 8 hours) is considered useful in the control of mucosal bleeding such as epistaxis, menorrhagia, gingival bleeding - although this is not supported by clear evidence. In clinical practice, 2 vials of 500 mg every 8 hours are administered orally (or intravenously) in adults. Antifibrinolytics should be avoided in case of hematuria.

Management of second or further line. The current guidelines, in the absence of direct comparison studies in

terms of risk/benefit, do not allow to establish any superiority among the three main therapeutic approaches: TPO-RA, rituximab and splenectomy. However, from a careful reading of the parts of the documents where the advantages and disadvantages of individual treatments are discussed in the context of good clinical practice, we can note a general preference of the authors for the use of TPO-RA compared to rituximab and even to splenectomy. Splenectomy, when it can be safely performed even from a hospital organizational point of view, remains a viable option even in the current pandemic situation. No evidence indicates an increased risk of contracting SARS-CoV-2 infection.

Among the two TPO-RA available in Italy (romiplostim and eltrombopag), in patients starting the treatment in COVID-19 period there is no preference between the two products. However for both a remote monitoring is recommended and self-treatment is suggested for patients treated with romiplostim. Moreover, in some local healthcare centers, delivery of both TPO-RAs to the patient's home has been activated, a valuable practice to be encouraged extensively. If patients are already in treatment at the time of COVID-19 pandemic, there is no reason to switch from one TPO-RA to the other, unless in case of loss of response to the agent in use. However, we should consider that the use of TPO-RA is associated with an increased thromboembolic risk,[18,19] which in case of development of COVID-19 infection could further increase. In case of inefficacy or intolerance to TPO-RA (around 70%), it seems reasonable to suggest as third line treatment the use of minimal doses of corticosteroids (≤ 10 mg / day) for the time strictly necessary, or immunosuppressants at the minimum effective dose, or possibly dapsone for centers that have experience with its use. In some patients, the combination of TPO-RA with low doses of steroids or immunosuppressants can restore a clinically effective platelet count, reducing the use of high doses of the individual active drug.

The administration of rituximab, even in reduced doses, is not recommended, also in compliance with what suggested by the authors of the UK and ASH guidelines. The latter - if in the individual case rituximab should be used in the absence of alternative therapies - recommend the possibility of administering plasma from donors recovering from COVID-19. Indeed, patients recently treated with rituximab (up to 6 months earlier) may not have adequate antibody response to the infection[20] and - more importantly - may not respond to COVID-19 vaccines. There are no data regarding the use of fostamatinib in patients with ITP and COVID-19. However its use in the treatment of severe COVID-19, in non-ITP patients is being considered of potential value[21,22] and, if its favorable effect is proved by prospective controlled trials, this agent could be an option in some refractory ITP patients at risk of bleeding.

Management of COVID-19 Positive Patients with Newly Diagnosed ITP or who Experience a Relapse of Previous ITP.

Paucisymptomatic patients not admitted into ICU. In paucisymptomatic COVID-19 patients who are not admitted to the ICU, we suggest the same approaches recommended by the guidelines for first-line treatment and reported above. However, without evidence on the effect of steroids on the course of COVID-19 infection, in patients without hemorrhagic manifestations, the general consensus, as a precaution, is to reduce the dosage and duration of administration (e.g. initial prednisone dose 20-25 mg/day regardless of body weight, with dose increase if necessary after 3-5 days, up to a maximum of 80 mg/day). In any case, prolonged administrations should be avoided, and tapering should be initiated within 2 weeks after the start of therapy. The use of IVIg is generally encouraged and could positively affect the evolution of the infection.[23] There is no contraindication to infusion of plasma obtained from patients recovering from COVID-19. However, hematologic consultation is required.

Patients admitted into ICU. Patients with ITP hospitalized for COVID-19, in internist wards and even more in the ICU, have numerous thromboembolic risk factors in addition to the infectious state (immobilization, respiratory failure, mechanical ventilation, use of central venous catheters). Moreover, COVID-19 infection with the associated cytokine and coagulation disorder is of particular concern in the absence of evidence on its treatment. For patients hospitalized in the ICU, each therapeutic intervention should be discussed, case by case, by the consultant hematologist and the intensivist. While the above suggestions for corticosteroids, IVIg and TPO-RA treatments remain generally valid, it should be noted that in patients receiving parenteral nutrition it could be advantageous to use a TPO-RA administered subcutaneously.

It should also be noted that on the basis of the results of the so-called Recovery Trial[24] the administration of 6 mg per day of dexamethasone (equivalent to about 60 mg of prednisone) for a maximum of 10 days, allowed to significantly reduce mortality at 28 days from randomization only in those patients who required invasive mechanical ventilation or simple assistance with oxygen, but not in those without the need for respiratory support. Particular attention should be paid to prophylaxis and possible antithrombotic treatment with LMWH or sodium heparin under continuous infusion in the ICU setting, and to the possible use of antifibrinolytic agents.

Thromboembolic risk and diffuse arterial microthrombosis. It is now well established that COVID-19 patients, even if only hospitalized, without the need to

be treated in the ICU, have a thromboembolic risk 3-4 times higher than internist patients in general, who have a risk estimated around 10%. Unexpectedly, even in initially asymptomatic cases a severe infectious picture can worse very rapidly, often complicating with a complex coagulopathy. This latter is clinically expressed with a further marked increase in thromboembolic risk, as well as with altered coagulation tests, and may be associated with the presence of microthrombi disseminated in the arterioles of various organs (heart, brain, kidneys), in a framework of diffuse endothelitis starting from the capillaries of the pulmonary alveoli.[9-11,25]

A systematic literature review with a meta-analysis of 66 clinical trials including 28,173 COVID-19-positive patients with a mean age of 62.6 years (60% males) showed an overall prevalence of VTE of 14.1%.[11] A subanalysis showed a prevalence of venous thromboembolism (VTE) of 22.7% in patients admitted to ICU and 7.9% in non-ICU patients. The prevalence of pulmonary embolism (PE) in ICU and non-ICU patients was 13.7 and 3.5%, respectively. A higher plasma level of D-dimers emerged as the only significant predictor for VTE.

In a series of 182 ICU patients with COVID-19 pneumonia, venous and arterial thromboembolic complications were identified in 31% of cases, in 81% of which represented by PE.[26]

In a single-center series of 198 patients treated in various medical departments (n=123) or in ICU (n=75) at the University of Amsterdam, thromboembolic events were studied, using objective methods, even in asymptomatic patients. VTE in patients with permanence in the ICU was much higher (47% equal to 35/75 up to 60-70% in cases of prolonged permanence in the ICU) than in patients hospitalized in internal medicine departments (3.2% equal to 4/124). In patients admitted to the ICU, the high incidence of thromboembolism was reduced by about half when only symptomatic patients were considered. This alarming frequency of thromboembolic complications occurred despite the fact that all patients were administered nadroparin at prophylactic doses and then had their doses doubled (ICU patients 2,850 I.U. antiXa twice a day if body weight <100 kg or 5700 I.U. antiXa twice a day if body weight ≥100 kg; in non-ICU patients half of the standard dose for surgical prophylaxis).[27]

In another study, conducted in China on 449 patients with severe COVID-19 with mortality around 30%, the use of LMWH in the 99 treated patients (22%) was shown to reduce mortality only in those with the most severe coagulopathy (60 to 40%), despite using prophylactic doses of enoxaparin (40-60 mg/day).[6] In both these studies, almost prophylactic doses were administered (apart from the ICU patients in the Dutch study), and therefore it remains to be determined whether an increase in heparin dosage was not preferable.

In any case, LMWH is not recommended even at prophylactic doses if the platelet count is < 30,000/μL; higher doses require a count > 50,000/μL. However, the use of LMWH in these cases should be shared with the physician/anesthesiologist treating the patient for COVID-19. Close monitoring is recommended with regard to both hemorrhagic risk, which is still increased even in severe patients with COVID-19 without thrombocytopenia, and thrombotic risk.

Venous and arterial thrombotic risk could be further enhanced in patients with previous splenectomy,[28] even more when treated with TPO-RA. On the other hand, the need for a generalized antithrombotic prophylaxis with LMWH and especially the need to use therapeutic doses, justifies the implementation of an appropriate therapy also with TPO-RA, in order to obtain a platelet count that allows antithrombotic treatments.

As mentioned above, we cannot exclude that in addition to classical thromboembolism, hemostatic abnormalities and hyper inflammation may result in the in situ formation of microthrombi at the level of the pulmonary vascular system, with subsequent extension of the phenomenon to the local pulmonary level and to other districts (heart, brain, kidneys).[9-11,29,30]

Given that COVID-19 coagulopathy is associated with intense fibrinolysis (as indicated by an exceedingly high D-dimers level) that may be protective,[31] the use of tranexamic acid should be reserved for patients with active bleeding and only after careful evaluation of the risk-benefit ratio in the individual patient, due to the possible protective mechanism of fibrinolysis, where plasmin formation can be either deleterious or beneficial.[32]

Accordingly, antifibrinolytics should be avoided in cases of evident DIC. The duration of treatment should be as short as possible. However, the relationship between COVID-19 infection and the coagulation and fibrinolytic system is an area of clinical research. The use of bedside diagnostic methods such as thromboelastography could be potentially useful in guiding the approach towards severe coagulopathy in patients admitted to the ICU[33] but further confirmatory data are needed.

Management of Patients with Chronic ITP.

In COVID-19 negative patients. In stable patients, with satisfactory response to current treatments, there is no need to make any particular changes from the second-line treatments proposed in paragraph *"Management of second or further line"*. Any change in therapy could result in increased risks, related to the need for more frequent monitoring and the possibility of a loss of response.

In COVID-19 positive patients. The same

recommendations proposed in paragraph *"Management of second or further line"* apply, recalling as a precaution the need to avoid high doses of corticosteroids or immunosuppressive drugs, unless strictly indicated by the treatment protocols adopted, even in the absence of direct evidence. The use of rituximab is definitively discouraged, for the reasons stated above, but if absolutely necessary the availability of plasma from donors recovering from COVID-19 should be preliminarily ascertained.

If a COVID-19 infection develops in a patient with ITP and platelet count falls to unsafe levels (< 10-20,000/μL), the recommended approach is the use of IVIg, possibly repeated as needed, reserving platelet transfusion for major bleeding. If the patient was already on TPO-RA, the dose could be increased to the maximum allowed. Short-term use of steroids (e.g., prednisone 1 mg/kg/day for 5 days), or possibly a cycle of dexamethasone (40 mg/day for 4 days) could also be considered.

To date, there are no data demonstrating an increased incidence of COVID-19 infection in patients with current or prior ITP, nor more severe manifestations of infection.

Splenectomized Patients. It is reasonable to assume that splenectomized patients do not have an increased risk of COVID-19 infection. However, they are more likely to be exposed to some bacterial infections. It is important to ascertain their vaccination status and if necessary revaccinate them for Pneumococcal, Meningococcal, and type b Hemophilus influenzae, as well as for seasonal flu. Moreover, should they not be on permanent prophylactic antibiotic therapy, as routinely prescribed in some countries (e.g. UK), it is recommended from the first onset of fever over 37.5°C, to start antibiotic therapy without delay, if possible preferably intravenous (e.g. amoxicillin combined with clavulanic acid).

If the situation does not show a rapid improvement, hospitalization is recommended because of the need for close surveillance and clinical and laboratory examinations, which must necessarily include blood culture tests. This recommendation derives from the possible occurrence (albeit very rare) of septicemia with acute or fulminant course and from the possibility of bacterial superinfections resistant to common antibiotics.

Pregnancy. The risk of adverse outcome during pregnancy in women with COVID-19 is estimated to be around 2.4%, and 1.8% for the newborn.[34,35]

Published epidemiological data indicate that, although the mortality due to COVID-19 in Italy was initially higher than in China, the prognosis of pregnant women in our country is comparable with that in China. An Italian study including 42 pregnancies in women positive for SARS-CoV-2, documented, out of 7000 deliveries observed between February and April 2020 in Lombardy, two preterm deliveries, seven accesses of pregnant women in the ICU with excellent resolution, and no fetal or neonatal deaths.[36] However, cases of vertical transmission from mother to fetus have been described in the literature.[37]

Therefore, even for pregnant women with ITP positive for SARS-CoV-2, the recommendations derived from the non-pregnant ITP population can be maintained, with the specific precautions adopted in pregnancy, in particular regarding contraindications to the use of TPO-RA and immunosuppressive drugs. A constant multidisciplinary approach is recommended for the pregnant woman with ITP, including the involvement of different specialists (hematologist, gynecologist, intensivist and infectious disease specialist).

There are no specific contraindications to pregnancy in COVID-19 negative ITP patients, for whom the commonly accepted indications in this setting are applicable. There is no contraindication to COVID-19 vaccine in pregnant women. Should de-novo ITP develop in a COVID-19 positive pregnant woman, steroids at lower than standard dose and immunoglobulins can be used as in current clinical practice.

Measures to Prevent Contagion. Scrupulous application of the indications on interpersonal distancing and on the use of masks and gloves are required. There are no specific contraindications about returning to work, if adequate protection measures against contagion are ensured. However, it is advisable to check with the referring hematologist.

Anti COVID-19 Vaccination. Since January 2021, an anti SARS-CoV-2 vaccination campaign has been launched in Europe and in particular in Italy, initially targeting health care workers and subsequently the most fragile categories of the population (elderly over 80 years, etc.), with priorities yet to be exactly established. The presence of current or previous ITP should not be a criterion for priority in vaccination.

Data on the two vaccines available at the date of writing (Pfizer and Moderna), are presented by two phase 3 papers published in the New England Journal of Medicine.[38,39] Although conducted in a relatively small number of individuals observed for a short period of time, these studies did not show specific side effects.

Immune thrombocytopenia, especially if in stable phase, should not represent a contraindication to vaccination. In patients with risk of bleeding after intramuscular administration (e.g., platelet count < 20,000/μL), adequate patient disclosure and possible prolonged observation are recommended.

Vaccination is strongly suggested for patients in whom treatment with rituximab or immunosuppressive agents is expected to be needed soon (to be administered,

if possible, at least one month before the start of these therapies).

Data on the use of the vaccine during pregnancy are currently very limited. Laboratory studies conducted on animals have not shown harmful effects during pregnancy. Although there are no specific recommendations based on clinical trials, vaccination is not contraindicated in an absolute way in pregnancy and, once the risk/benefit ratio has been positively assessed during the patient's consultation with the hematologist, the infectious disease specialist and the gynecologist, it can be considered feasible. The same considerations apply to breastfeeding women.[40,41] In this regard, see also the links to AIFA FAQ (in Italian) and CDC recommendations.[42,43]

Additional Note: The Authors of these guidelines recommend that, despite the COVID-19 pandemic, all involved centers continue to actively participate without interruption to all company or investigator-driven clinical trials exploring the safety and efficacy of new drugs for ITP, possibly also using direct contact with patients, by means of electronic communications or by phone. In particular, the following drugs in phase III studies are of primary interest: FcRn inhibitors like efgartigimod (Argenx) or rozanolixizumab (UCB); rilzabrutinib (Principia) and a reversible inhibitor of Bruton Tyrosine Kinase (TAK-079/ mezagitamab (Takeda) an inhibitor of CD 38 cells, still in phase II).

Similarly, there is a need to continue to enroll patients into the national registries and to participate in "real word studies" exploring traditional approaches, such as those based on the various TPO-RA and on the recently introduced Syc inhibitor (Fostamatinib).

Updated information on new and old drugs is even more relevant since this pandemic reveals that precision medicine should be adopted and that all current treatments have some limitations.

Caveat. This document, updated to 27 April 2021, is limited to offer general suggestions and it remains the responsibility of the individual hematologist to adapt them to the individual patient.

Regarding potential SARS-CoV-2 vaccine–risk, last release updates from EMA should be considered (https://www.ema.europa.eu/en). Unfortunately, recently rare cases of massive disseminated thrombosis often accompanied by severe to moderate thrombocytopenia or DIC have been reported. This new syndrome manifests with venous sinus thrombosis (CVST) and/or splanchnic venous thrombosis and in some cases also with venous or arterial thromboembolism. So far, the occurrence of this severe complication, not rarely resulting in death, has been described only with DNA recombinant vaccines using adenoviral vector encoding the spike protein of SARS-CoV-2.

Initially described in association with the first dose of AstraZeneca vaccine (Vaxzevria), mostly in women younger than 55 years, more recently, similar events were also reported after Janssen (Johnson&Johnson) vaccine, apparently at a lower rate. While Vaxzevria uses a chimpanzee adenovirus as vector (ChAdOx1 nCoV-19), Janssen (Johnson&Johnson) uses a human one (Ad26.COV2.S). Occasionally, atypical thrombosis has been reported also with RNA-based vaccines.

Given the rarity of the events, the strength of any association is not yet definitely proven and the benefits of vaccination still outweigh the risks. For more information on Vaxzevria visit the EMA safety committee (PRAC) press release of 7 April 2021 at https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood and of 13 April 2021 at https://www.ema.europa.eu/en/medicines/dhpc/vaxzevria-previously-covid-19-vaccine-astrazeneca-link-between-vaccine-occurrence-thrombosis.

For Johnson & Johnson vaccine, visit https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-janssen-epar-product-information_en.pdf, updated at 22 April 2021. A Eudra Vigilance report as of 4 April 2021 includes a total of 169 cases of CVST and 53 cases of splanchnic vein thrombosis with Vaxzevria vaccine. Around 34 million people have been vaccinated in the EEA (Economic European Area) and UK by this date. The more recent data do not change the EHA PRAC recommendations. Recently, three articles and an Editorial paper were published in a leading medical journal describing 39 cases associated with the newly described syndrome, characterized by thrombosis and thrombocytopenia, that developed 5 to 24 days after initial vaccination with Vaxzevria.[44-47] The pathogenic mechanism of this new entity called Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) seems related to the induction of autoantibodies against platelet factor 4 (PF-4)-polyanion complexes. This is similar to heparin induced thrombocytopenia (HIT), in which PF-4-heparin complexes are the target of the autoantibodies that inappropriately activate platelets inducing thrombocytopenia and thrombosis. It is recommended to avoid heparin and to prefer other anticoagulants, like fondaparinux. High doses of corticosteroids and IVIG are suggested as the most effective treatment for the correction of the accompanying severe thrombocytopenia in order to control or prevent cerebral hemorrhages, often the leading cause of death in CVST.

Currently, different European Countries are following specific policies of vaccination that may deviate from EMA precise indications and the treating

physician is required to access the most updated information from the competent national regulatory agencies.

At this moment in Italy both the DNA recombinant vaccines are preferably administered to people aging 60 or more (https://www.aifa.gov.it/domande-e-risposte-su-vaccini-vettore-virale). Fortunately, so far no cases of VITT have been reported in patients with past or ongoing ITP.

In addition to VITT, some cases of "typical" ITP with or without bleeding, but without thrombosis, have been reported as induced by or revealed after exposure to the messenger RNA (mRNA)–based vaccines as those produced by Moderna (mRNA-1273) and Pfizer–BioNTech (BNT162b2).[44,48] This is not of major surprise, considering that similar rare cases have been observed after "traditional" vaccine administration against other infectious agents and could thus be expected. In this regard, a study is ongoing in Italy to better evaluate the frequency and severity of isolated thrombocytopenia with or without bleeding occurring after COVID-19 vaccination.

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