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THE CoV-2 OUTBREAK: HOW HEMATOLOGISTS COULD HELP TO FIGHT COVID-19.

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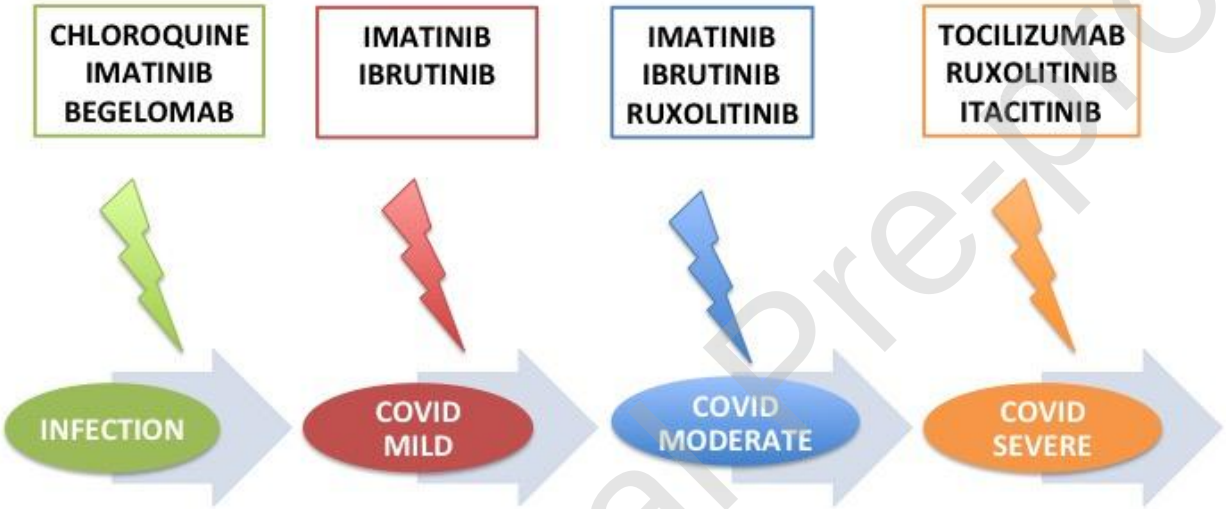
Graphical abstract

GRAPHICAL ABSTRACT



ABSTRACT

COVID-19 is a medical emergency, with 20% of patients presenting with severe clinical manifestations. From the pathogenetic point of view, COVID-19 mimics two other well-known diseases characterized by cytokine storm and hyper-activation of the immune response, with consequent organ damage: acute graft-versus-host disease (aGVHD) and macrophage activation syndrome (MAS). Hematologists are confident with these situations requiring a prompt therapeutic approach for switching off the uncontrolled cytokine release; here, we discuss pros and cons of drugs that are already

employed in hematology in the light of their possible application in COVID-19. The most promising drugs might be: Ruxolitinib, a JAK1/2 inhibitor, with a rapid and powerful anti-cytokine effect, tyrosine kinase inhibitors (TKIs), with their good anti-inflammatory properties, and perhaps the anti-Cd26 antibody Begelomab. We also present immunological data from gene expression experiments where TKIs resulted effective anti-inflammatory and pro-immune drugs. A possible combined treatment algorithm for COVID-19 is here proposed.

Keywords**:** COVID-19, Ruxolitinib, TKIs, Begelomab, Baricitinib, Tocilizumab, GVHD, MAS

INTRODUCTION.

Coronavirus disease 2019 (COVID-19), sustained by the new Coronavirus SARS-CoV-2, started in China in December 2019 in the province of Hubei and then rapidly overspread over the world, becoming a “pandemic”. The 22 April 2020, the European Centre for Disease Prevention and Control reported 2,520,522 infected subjects around the world, with 176,786 deaths [https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases]; 1,101,681 people were infected in Europe and 825,041 in USA, with 107,453 and 45,063 deaths, in Europe and USA, respectively [https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html].

This great number of infected subjects is requiring an enormous worldwide effort for hospitalizing and caring all patients who have to receive firstly an adequate diagnostic approach (chest X-ray or CT, viral genome identification and quantitation, serology), then the best possible therapies that might avoid the more severe phase of disease. From the clinical point of view, the majority of patients remains asymptomatic or presents mild symptoms; Mizumoto et al. conducted an epidemiologic study on the 3,711 people who remained on board of the Diamond Princess cruise ship, blocked in Japan after identification of a SARS-CoV-2-positive passenger; these authors estimated that 17.9% of all infected cases remained asymptomatic during quarantine [1]. Another group estimated that the rate of symptomatic cases was 101/10,000, after a median incubation time of 14 days [2]. Moreover, the Italian COVID-19 Surveillance Group, during the peak of infection, reported 460 deaths on 85,308 infected individuals (9.9%), with an overall case-fatality rate around 7.2%, substantially

higher than in China (2.3%), thus highlighting the compelling need for more effective approaches. The median age of infected subjects was 62 years, 85% of deaths occurring in patients between 70 and 89 years. Moreover, only 1.2% of infected patients presented at the hospitalization without comorbidities, while 23.5% had one, 26.6% two, and 48.6% three or more comorbidities. The most frequent concomitant diseases resulted: previous ischemic heart attack or stroke, atrial fibrillation, hypertension, diabetes, dementia, a recent history of cancer, chronic liver disease or renal failure. Only 7.5% of patients did not present any symptom at the hospital admission, 12.7% were pauci-symptomatic, 37.9% and 19.6% manifested mild and severe symptoms, respectively, while 4.4% were critical [https://www.epicentro.iss.it/coronavirus/]. In the international scenario, the most frequent clinical manifestations were fever and dyspnea, whilst cough, diarrhea and hemoptysis were less common; acute respiratory distress syndrome (ARDS) was observed in 96% of severe cases, followed by acute renal failure in one third of them; super-infections were documented in 8.5% of critical cases where septic shock and the macrophage activation syndrome (MAS) were the most frequent cause of death [3,4]. From the early stages of infection patients develop lymphopenia and neutrophilia; in the more advanced cases, lymphocyte further reduce, liver failure appears with hypoalbuminemia, and the hyper-inflammatory status, characterized by high levels of reactive protein C, ferritin, D-dimer, LDH, troponin and N-terminal fragment of the B-type natriuretic peptide (NT-proBNP), is demonstrable [5,6].

The pathogenesis of this “hyper-inflammation” have been recently revised: chemokines, such as MCP-1, IL2, IL-7, IL-10, G-CSF, IP-10, MIP-1A and IL6 are highly expressed, whereas TNF-alpha seems to be only moderately up-regulated. Cytotoxic CD8+ and exhausted T cells, together with an abnormal balance between Th1 and Th2 lymphocytes, mirror the onset of a severe immune dysfunction [7]. Consequently, several approaches able to switch off inflammation by maintaining at the same time the host’s antiviral immunocompetence have been rapidly designed and tempted: **Chloroquine**, already employed in rheumatological diseases, inhibiting the attack of the SARS-CoV-2 to the ACE2 receptors (that represent one of the two virus receptors) resulted quite effective [8], alone or in combination with azithromycin [9]. **Tocilizumab**, an anti-IL6 antibody, already used both in rheumatoid arthritis [10,11] and in the cytokines release syndrome after infusion of CAR-T in patients affected by acute lymphoblastic leukemia or aggressive lymphomas [12,13], has been employed with success in COVID-19. Recently, an Italian group proposed a new treatment algorithm whose backbone is represented by

Chloroquine; Tocilizumab is used precociously in all patients with high levels of IL6 and D-dimer, including those, especially the elderly cases, with hypoxemia without severe dyspnea [14]. Other possible options from the "rheumatological" background are the anti-IL1 monoclonal antibody **Anakinra**, already effective in the MAS [15], and the JAK1/2 inhibitors, such as **Baricitinib**, already employed in rheumatoid arthritis [16], used alone or in combination with intravenous Immunoglobulins [14]. In 22 April 2020 a clinical trial aimed to assess the Baricitinib effectiveness in severe COVID-19 has been authorized by the Italian Drug Agency (AIFA) [https://www.aifa.gov.it/sperimentazioni-cliniche-covid-19]. Finally, anti-TNF alpha antibodies, such as **Adalimumab**, prescribed for the treatment of psoriasis [17] and Behcet's disease [18], have been proposed as possible furher therapeutic tools for COVID-19 pandemic [7].

In this apocalyptic scenario, some authors already observed that this "rheumatological" approach, notwithstanding a clear fast and positive anti-inflammatory effect, could impair the immunological control of neoplasms in patients receiving chemotherapy or immunotherapy for cancer. Indeed, cancer patients showed a higher rate of severe events after SARS-CoV-2 infection in comparison with patients without cancer (39% vs 8%) [19]. This epidemiological observation, in addition to the consideration that the majority of reported comorbidities in patients with critical COVID-19 were diseases characterized by a pro-inflammatory profile, underlines once again the need of identifying further drugs exerting a significant anti-inflammatory action but without losing their anti-tumor effect. On the basis of these considerations, we decided to review literature and what hematologists know about the relationship between hematological drugs, inflammation and immunity, in order to help the scientific community to definitively fight the COVID-19.

1. COVID-19 challenge: what hematologists learnt from hematological diseases.

1.1 Two good "hematological" COVID-19-like models: the graft-versus-host disease and the MAS.

In hematology, we have a well-known similar condition that mimics the hyper-inflammation caused by the new Coronavirus: the **graft-versus-host disease**, in its acute (aGVHD) and chronic forms (cGVHD). GVHD, which interests about half of transplanted patients, can appear by or after 100 days from the allogeneic stem cell infusion, with a prevalence that ranges from 35% to 55%, according to donor type, conditioning regimen, disease status at transplant and prophylactic approach

[20,21]. GVHD is the consequence of a misleading attack by donor T lymphocytes of several recipient's antigens recognized as outsiders, with consequent damage of his/her liver, lungs, gastrointestinal tract, eyes, vagina, muscles and joints. Allogeneic T and B lymphocytes sustain this hyper-inflammation that causes tissue damage and fibrosis, both by increasing production of inflammatory cytokines (IL-1, IL-2R, IL-6, TNF alpha) and by the deposition of immune complexes. The intestinal epithelium damage releases bacteria and modifies the gut microbiome, further increasing the immune response: T CD8+ lymphocytes are especially activated by the recipient hematopoietic antigen-presenting cells (APC), whereas donor T CD4+ cells can be activated by other APC types, principally in the gut. The participation of other immunocompetent cells, such as NK, macrophages, monocytes and neutrophils, makes GVHD a hyper-inflammatory dangerous condition that well recapitulates what occurs in COVID-19, where the rapid Coronavirus replication impairs the IFN-induced immune response, with rapid increase of M1-oriented macrophages and pro-inflammatory cytokines [7]. Moreover, clinical manifestations, especially of the aGVHD, are similar to those observed in COVID-19: skin rash, diarrhea, elevated bilirubin, infections, pulmonary leak syndrome, eye and mouth damage and, in the chronic form, also fasciitis, myositis and fibrosis that mimic the systemic scleroderma [22,23].

Another COVID-19-like condition that hematologists and rheumatologists have to deal with is the Macrophage activation syndrome (**MAS**), an acute hyper-inflammatory condition characterized by activation and expansion of T cells and hemophagocytic macrophages, with the consequent cytokine storm, with increased levels of proinflammatory cytokines, such as IL-1, IL-6, IL-18, TNF alpha, and IFN gamma [24]. MAS is reported to interest about 4% of patients with juvenile idiopathic arthritis and systemic lupus erythematosus, but it can also represent a complication of hematological neoplasms or infections, with a mortality higher than 40%, that makes MAS a real medical emergency [25]. From the diagnostic point of view, MAS is a febrile condition characterized by hyperferritinemia, multilineage cytopenia, coagulopathy, transaminitis, high levels of triglycerides, hypofibrinogenemia and splenomegaly. Classically, MAS is treated with high steroid doses and etoposide [26], but in the era of new biological drugs promising results derived from the use of anti-IL1 and anti-IL6 antibodies, like Anakinra, Canakinumab, Rilonacept and Tocilizumab [27].

2. The hematological approach to COVID-19: pros and cons.

Hematologists are already confident with GVHD and MAS, that require a rapid intervention for switching off the cytokine storm and controlling the exaggerated immune response. In the following, we'll discuss positive and negative aspects of drugs employed for treating GVHD and MAS, in the light of their possible employ in the COVID-19 war.

2.1 Immunosuppressive agents. In aGVHD, treatment includes topic or systemic corticosteroids, anti-thymocyte immunoglobulins, cyclosporine, mycophenolate mofetil for appropriate management of acute phase. Novel approaches also include mesenchymal stem cells, etanercept and infliximab (anti-TNF alfa), daclizumab (anti-IL2) or vedolizumab (anti-a4b7), but results are still very preliminary and not worth to be considered for translating the experience deriving from the aGVHD "new era" directly to the COVID-19 [28]. About cGVHD as "inspirating source", also in this case the first line approach is represented by immunosuppressive agents [29] that seems to be *not really effective in COVID*-19 [7].

2.2 Monoclonal antibodies. Tocilizumab, anti-IL6 monoclonal antibody, has been used also for treating aGVHD**,** with 70% of partial remissions (PR). Nevertheless, in a series of 11 patients, 2 developed a bacterial sepsis, one of whom died [30]. Until today, 23 trials have been registered in the "clinical trials.gov" website, *thus supporting the promising use of this drug in COVID-19*. **Rituximab** has been also used as therapeutic tool in GVHD, with 60% of overall response rate (ORR); however, as reported by the Italian cooperative group (GITMO), 3/38 treated patients died for infections [31], and in a meta-analysis involving 111 cGVHD patients, one third of them presented pneumonitis and Herpes virus reactivation [32]. No studies involving this monoclonal antibody have still registered in the "clinical trials.gov" website. *In our opinion, the use of Rituximab in the COVID19 could be not considered, either for the high rate of infections reported in the hematological context, or because Rituximab requires a too long time to be efficacious.*

Begelomab, a monoclonal anti-CD26 antibody, has been recently reported to be efficacious in treatment of 69 steroid-refractory aGVHD patients. In the compassionate use, Begelomab was administered at 3 mg/m^2/day for 5 days, followed by six additional doses of 3 mg/m^2 at day +10, +14, +17, +21, and +24. The overall response rate at one month was 75% in the prospective studies and 61% in the compassionate use, with complete response rates of 11 and 12%, respectively. Response in grade-III GVHD was higher than 70%, and response in grade-IV GVHD cases about 60%, with higher response rates described for skin, liver, and gut. The tolerability of treatment was good, with the most common adverse

events being diarrhea, cytomegalovirus reactivation, infections, probably more linked to the GVHD and the previous steroid treatment than to the antibody itself. In the 8 complete responders there was only one late death due to infections; in the 38 partial responders, the infection rate was 10.5% [33]. Recently, the DPP4/CD26 glycoprotein has been reported to be one of the two receptors for the spike S1 SARS-CoV2 surface protein, together with the angiotensin converting enzyme (ACE2) [34]. Once activated by SARS-CoV-2, this protease helps virus 1) to reduce autophagy, the process physiologically aimed to eliminate external microorganisms from the host cells, 2) to sustain the hyper-inflammatory status and 3) to reduce the host anti-viral immune response [35]. The hypothesis of destroying this strict link by the anti-CD26 antibodies or the DPP4 inhibitors, already employed in the diabetic patients, seems really interesting [36]. DPP4 inhibitors have been already demonstrated to be efficacious in several *in vitro* models of SARS [34] and, considering the 80% of homology between old and new Coronavirus, DPP4 inhibitors might be useful also in the COVID-19 pandemic [37]. Nevertheless, no studies with Begelomab have still been registered in the "clinical trials.gov" website. *Considering these novel findings about the possibility of destroying the CD26 axis connecting Coronavirus and inflammation/perturbed host immunity, in our opinion, the use of Begelomab, probably for a short time course, might be considered an interesting approach, worth to be tested in the COVID19.*

2.3 BTK inhibitors. In the last two years, FDA and EMA licensed Ibrutinib as treatment for steroid-refractory cGVHD. **Ibrutinib**, already effective in high risk chronic lymphocytic leukemia (CLL) [34], in addition to the Bruton Kinase, also inhibits another kinase, the interleukin-2–inducible T-cell kinase (ITK), that is involved in the selective activation of T-cells that drive immune reactivity toward healthy tissues [38], and a SRC kinase, HCK, whose over-expression, in a murine model, has been reported to be responsible for extensive pulmonary inflammation and enhanced immune response, particularly in older mice [39]. In cGVHD, Ibrutinib, switching off the cytokine storm, was successful in two third of cases, with 21% of complete and 45% of partial responses [40], with a significant improvement of patients' quality of life [41]. Unfortunately, this treatment is characterized by adverse events that cause treatment discontinuation in 30% of patients; in particular, pneumonitis, fatigue and diarrhea of grade ≥3 occur in 71% of patients in the first year and in 25% in the second year, inducing therapy discontinuation in 40% of cases [38]. In agreement with these results, the experience in CLL reported

high infection rates: in a cohort of 378 patients, serious infections were observed in 11.4% of cases, especially bacterial and fungal [42]. At the moment, no clinical trials using Ibrutinib in COVID-19 have been registered in the “clinical trials.gov” website; nevertheless, Treon and coworkers in the last days published in Blood an interesting report concerning the low rate of COVID-19 occurrence in patients with Waldenstrom’s macroglobulinemia (only 6 out of 300 individuals). All patients experienced cough and fever as prodromal symptoms; the 5 patients on Ibrutinib 420 mg/day experienced no dyspnea and did not require hospitalization, with a shorter disease course in comparison with the one patient receiving lower Ibrutinib dose, who, on the contrary, required the administration of Tocilizumab and i.v. immunoglobulins [43].

In our opinion, Ibrutinib, might be a potential candidate for fighting the CoV-2, but probably if used for a short time, due to the high number of infections and treatment discontinuations that usually characterize its use in the hematological scenario. Clinical trials are needed to conclude if the balance weighs more on the side of efficacy or toxicity.

2.4 JAK2 Inhibitors. The other drug licensed by FDA and EMA for treatment of GVHD is **Ruxolitinib**, already successfully employed for reducing spleen dimension and improving quality of life and survival of patients affected by myelofibrosis [44]. Ruxolitinib, a JAK1/2-inhibitor, decreases the activity of Th1 lymphocytes, and, through modulation of the STAT pathway, the secretion of pro-inflammatory cytokines, such as TNF alpha, IL1, IL6, and IFN gamma [45]. Ruxolitinib is effective both in acute and in chronic GVHD: in 71 cases of steroid-refractory aGVHD, Ruxolitinib offered 55% of ORR and 27% of CR, especially in skin, gastrointestinal tract, and liver. Median duration of response was 345 days and the overall survival (OS) at 6 months 51.0%. Cytopenias occurred in half of cases, peripheral edema in 45%, but no significant infective toxicity has been reported [46]. In another cohort, Ruxolitinib, at a dose of 20 mg/day, offered 57.1% of ORR; reported adverse events were anemia, thrombocytopenia, neutropenia, infections, edema, bleeding, and transaminitis [47]. In the cGVHD, Ruxolitinib has been reported to be effective in 80% of patients; nevertheless, reactivation of CMV occurred in 15% of patients [48]. In a meta-analysis including 414 patients with cGVHD, during treatment with Ruxolitinib infections occurred in 20% of patients, more frequently sustained by bacteria (55%) and CMV (39%) [49]. The pro-infective aspect of Ruxolitinib is also evident in myelofibrosis, where cases of hepatitis B [50] and tuberculosis (in 1.4% of cases) [51] reactivation, in addition to pneumonitis sustained by *Pneumocystis jiroveci* [52], have been reported. In the last weeks, 8 clinical trials with Ruxolitinib

in COVID-19 started, with dose ranging from 10 to 20 mg/day. The first 11 cases treated in Italy avoided the incoming intubation, so confirming in the real life the anti-inflammatory power of this JAK1/2 inhibitor.

In our opinion, Ruxolitinib could represent a very good candidate against COVID-19 for its well-known powerful and fast anti-inflammatory effect; nevertheless, the high rate of viral and microbial reactivation observed in the hematological setting might represent a caveat in its prolonged use in the COVID-19.

2.5 Tyrosine kinase inhibitors. Another class of drugs already employed in the treatment of GVHD that could help to win the COVID-19 challenge are the tyrosine kinase inhibitors (TKIs), already successfully employed in treatment of chronic myeloid leukemia (CML), Philadelphia-positive acute lymphoblastic leukemia and stromal gastro-intestinal tumor (GIST) [53]. Imatinib has been the first TKI licensed for CML treatment, followed by Nilotinib, Dasatinib, Bosutinib (second generation TKIs) and Ponatinib (third generation TKI). All TKIs, and especially those of second and third generation, in CML offer high rates of complete hematological, cytogenetic and molecular responses [53], necessary key for treatment discontinuation (TFR), that has success in about 40% of patients [54]. Different studies focused on TFR explored the impact of TKIs on the immunological response, showing that this class of drugs play a positive effect on NK cells whose number and activated status is fundamental for maintaining deep molecular response without treatment [55,56]. Moreover, TKIs are able to restore the immunocompromised status observed in CML patients at diagnosis by reducing myeloid-derived suppressor cells, re-activating T and NK cells, and reducing the expression of PD-1 on T and NK lymphocytes and of PD-L1 on the microenvironment and on neoplastic clone [57]. **Imatinib** has been employed with success also in GVHD, but mainly in its chronic form, where it was successful in about 60% of cases [58]. From the safety point of view, in a series of 19 cases only one pneumonitis and one CNS infection by JCV have been reported [59]. In another cohort with sclerodermic GVHD Imatinib was compared to Dasatinib: one of the 4 patients receiving Imatinib had pneumonitis versus 2 of the 5 cases treated with Dasatinib [60]. Two trials proposing Imatinib in COVID-19 have been already registered in the “clinical trials.gov” website (NCT04357613, NCT04356495), both involving elderly patients. In a third study, Imatinib will be compared to hidroxicloroquine, Lopinavir/ritonavir, and Baricitinib (NCT04346147).

In our opinion, Imatinib might represent a good therapeutic possibility in the COVID-19 for its demonstrated anti-inflammatory activity added to a good safety profile, but a caveat has to be done about the delayed onset of its positive therapeutic effects.

Dasatinib has not been further used in GVHD, but the toxicities that it causes in CML might contraindicate its use in the COVID-19. In fact, about 25% of CML patients develop pleural effusion during Dasatinib treatment [61]. Several mechanisms have been explored, from the inhibition of PDGFR beta to increased T lymphocytes in pleural fluid [62]**.** In multivariate analysis, a previous skin rash or history of autoimmune disease resulted as significant factors predicting pleural effusion [63]. About infective risk during Dasatinib administration, the incidence of grade 3/4 infections resulted 11% [64]; in the DASISION trial, which compared Dasatinib with Imatinib as first-line treatment, 4.5% of patients in the Dasatinib and lessa than 1% in the Imatinib cohort died for infections, so sustaining the high infective risk of Dasatinib in comparison to Imatinib [65]. At the moment, no studies with Dasatinib in COVID-19 have been registered in the "clinical trials.gov" website. On the basis of available data, *in our opinion, Dasatinib might be not a valid candidate for the COVID-19 treatment.*

On the contrary, different promising suggestions come from some *in vitro* and *in vivo* models that would support the use of **Bosutinib** as a powerful anti-inflammatory agent. This TKI is today indicated for treatment of CML Imatinib-intolerant or resistant patients [66]. Differing from Dasatinib, whose pro-inflammatory action is supported by the high rate of pleural effusion, Bosutinib resolved this adverse event in 17/20 cases presenting effusion during treatment with Dasatinib. Moreover, the safety of Bosutinib from the immunological point of view is supported by the quite total absence of infective adverse events [67]. Moreover, in a model of membranous glomerulonephritis, Bosutinib was able to ameliorate renal damage by reducing expression of IL2R, IL4R, and by inhibiting JAK2/JAK3 (that sustain the inflammatory pathway) [68]. In another murine model of intra-cerebral hemorrhage with brain injury caused by post-bleeding inflammation, Bosutinib once more showed its anti-inflammatory action: inhibiting SIK-2, it activates CREB and IkB, so blocking the NF-kB-derived inflammation. Moreover, Bosutinib shifted the macrophagic response from M1 to M2, and decreased pro-inflammatory cytokines production [69]. Bosutinib and Nilotinib were also used and compared in a murine model of Alzheimer's disease (where brain plaques are considered a consequence of hyper-inflammation). In this context, both TKIs decreased

inflammation by reducing TNF alpha, IL4, IL6, IL3, and IL2 levels and increasing IL10 and CX3CL1, but, in comparison with Nilotinib, Bosutinib increased IL-10 and CX3CL1 also in the peripheral blood [70]. Thus, the anti-inflammatory profile of Bosutinib is evident. About its safety, in the BEFORE trial, where Bosutinib and Imatinib were compared in 536 CML patients in first line, grade 3/4 infection rate was 3.4% in the Bosutinib versus 4.9% in the Imatinib arm, with only 0.4% of upper respiratory tract infections in the cohort treated with Bosutinib [71]. All these data suggest that Bosutinib might have a relevant anti-inflammatory effect, with a good safety profile; at the moment, no studies with Bosutinib have been registered in the "clinical trials.gov" website. *Nevertheless, in our opinion, Bosutinib could be considered a possible effective drug in the COVID-19. Nevertheless, no experience with this drug has been done in GVHD or MAS.*

Nilotinib is a valid second-generation TKI approved for treatment of CML in first or subsequent lines [72]. Nilotinib is now in experimentation also in GVHD, on the basis of data from the preclinical studies that clearly demonstrated its anti-inflammatory power. Indeed, Nilotinib significantly reduced production of pro-inflammatory cytokines (IL-2, IFN-gamma, TNF alpha, IL-17, TGF beta), without losing the lymphocyte immunocompetence [73,74]. Nevertheless, no definitive data on Nilotinib safety in GVHD are still available; consequently, safety profile must be derived from the experience in CML. In the ENESTnd trial, comparing Nilotinib and Imatinib in 564 CML patients in first line, all grade infection rate was 17% in the Nilotinib versus 14% in the Imatinib arm, with grade 3/4 infections rate in the Nilotinib cohort less then 1% [75]. In conclusion, Nilotinib seems to be an anti-inflammatory agent with a good infective safe profile; these features could make it, in our opinion, a good candidate in the COVID-19 setting; nevertheless, we have to consider its high rate of cardiovascular complications seen in CML [76,77] that could be the consequence of the inflammatory endothelial damage, as shown by higher IL6 and lower IL10 levels in CML patients presenting cardiovascular events [78]. At the moment, no studies with Nilotinib in COVID-19 have been registered in the "clinical trials.gov" website. *In our opinion, this pro-atherogenic aspect might made Nilotinib a sub-optimal candidate in the COVID-19 context.*

2.6 Interferons.

Interferons (IFNs) are old, but at the same time “evergreen” drugs, for many years used for treating different hematological diseases, from CML and Philadelphia-negative chronic myeloproliferative neoplasms (MPNs) to lymphomas and myeloma, due to their potent immune enhancing capacity that allows recognition and elimination of neoplastic cells by the patient’s immune system. In CML, Interferon has been used until the introduction of TKIs; its offered hematological and cytogenetical, but very few molecular responses. Nevertheless, for many years it represented an advantageous treatment in respect of hydroxyurea [79]. In MPNs, IFNs are still successfully employed, especially in younger people, where their discontinuation after long-term treatment may be followed by several years with normal cell counts and low-JAK2V617F burden, that once again supports the concept that IFN-alpha is able to modulate and enhance the immune system-mediated defense against cancer [80]. In lymphomas, IFN is still the first line of treatment of hairy cell leukemia [81] and, with less fortune, has been employed as maintenance therapy in indolent lymphomas, especially after autologous transplantation [82]. In multiple myeloma, IFN has been demonstrated to reduce plasmacells growth by down-regulating the IL6 production, with a synergic action with melphalan and corticosteroids in reducing the monoclonal component. IFN has also been used as maintenance after autologous transplantation before introduction in the clinical practice of lenalidomide and bortezomib, but with doubt favorable prognostic impact [83]. Moving from the hematological context to the SARS, during the outbreak of 2002 IFNs were also tried; a meta-analysis including 54 studies with IFN was performed in 2006, with discordant results. Indeed, while the *in vitro* studies showed a good anti-viral power of IFNs (with IFN beta being more effective than alpha), the *in vivo* studies were inconclusive, with a doubtful prognostic advantage in respect of steroids [84]. At the moment, 6 studies, aimed to understand if IFNs might be useful in COVID-19, have been registered in the “clinical trials.gov” website, trying either IFN alpha/beta or lambda (NCT04344600, NCT04350671, NCT04343768, NCT04343976, NCT04254874, NCT04320238). Interestingly, one of these studies is employing the IFN alpha via aeresol, probably in order to avoid the systemic adverse events (flu-like syndrome, fatigue, hypothyroidism, creatinine increase) that frequently lead to the drug discontinuation in the hematological patients [85]. The use of IFN lambda (type III IFN), seems interesting, based on different action mechanisms that characterize tipe I and III IFNs. Indeed, for decades, type I IFNs (IFN alpha and beta) have been explored as mediators of rapid, innate antiviral protection. In 2003, a novel group of three cytokines, now known as type III IFNs (IFN lambda), have been discovered. The distinctive actions of type I and type III IFNs depend on the engagement of different receptors:

type I IFNs trigger pro-inflammatory responses via the recruitment and activation of immune cells, promoting an anti-viral state in the host, while type III IFNs signal is restricted to epithelial cells and neutrophils. Therefore, type III IFN administration as a prophylactic treatment or at an early stage of COVID-19 might result in a good antiviral response localized to epithelial cells, reducing side effects and inflammation associated with the systemic action of type I IFNs [86] *In our opinion, considering the actual availability of different clinical options, because of their poor tolerability, IFNs might be not good candidate in the COVID-19 therapy.*

3. Our personal contribution to the COVID-19 war: the analysis of the immune transcriptome.

After this analysis, we became convinced that, in addition to Ruxolitinib, Imatinib and Bosutinib would represent possible interesting therapeutic tools in the COVID-19 war. Thus, we decided to contribute to the COVID-19 challenge by confirming *ex vivo* the anti-inflammatory power of Imatinib and if and how it could modify the immunological profile of our patients. Thus, we used the Nanostring technology (Nanostring, Seattle, USA) for analyzing the immune transcriptome profile of 5 patients affected by CML, at diagnosis and after 6 months of treatment with Imatinib. The tested RNAs have been already stocked in our laboratory as leftovers that the respective patients donated to us for further non-profit researches after routine diagnostics. We employed the “Human nCounter Myeloid Innate Immunity panel” that measures the expression value of 770 genes involved in 19 different pathways fundamental for the innate immune response. Results were analyzed by the nCounter Advanced Analysis 2.0 software. In Figure 1 we represented some of the up- (red squares) and down-regulated (green squares) genes by volcano plots, and in the Table 1 are listed all down- (in green) or up- (in red) regulated genes and the pathways where they are involved. In Table 2 we better detailed all genes that resulted significantly deregulated after Imatinib, their respective physiological role and their possible contribution to inflammation and immunological infection control. Overall, 40 genes resulted down- and 18 up-regulated by Imatinib; 35 of these down-regulated genes may sustain the inflammation in different autoimmune diseases, whilst 5 are anti-inflammatory. After Imatinib-induced gene expression down-regulation, the final effect was a significant reduction of pro-inflammatory cytokines and chemokines mRNAs. Unfortunately, these data are not completed by the quantification of cytokines in the serum, because of the retrospective

nature of the study. On the other hand, among the 18 genes those expressions increased after Imatinib, 15 support the physiological innate immune response. More in detail, among the down-regulated ones, we found some genes that are highly expressed in autoimmune diseases: ANX4A, high in the Sjogren's syndrome [87], CASP10, high the Crohn's disease [88], while CEACAM8 [89], CTSG [90], and IL18 [91] are overexpressed in arthritis. Moreover, CLEC5A, increased after neurogenic shock [92], CXCL2 and GRN are highly expressed in the Alzheimer's disease [93,94], ITGAM was elevated in psoriasis [95], and PGLYRP1 had high levels in chronic gingivitis [96]. All these genes were down-regulated by Imatinib, as a demonstration of its anti-inflammatory action. At the same time, the anti-inflammatory effect exerted by Imatinib was also sustained by the reduced expression of the genes that identified the mast cells (Figure 2). Our Nanostring analysis also demonstrated that, while Imatinib reduced inflammation, the patient's immunocompetence was not lost. Indeed, Imatinib down-regulated several genes that physiologically impair the T- and NK-cell response, such as ARG1 [97], C3AR1 [98], CEACAM1 [99], GSN [100] and NECTIN1 [101]. On the contrary, this TKI up-regulated some genes that usually support the immune response, such as JAK3, able to switch the macrophagic response from M1 (pro-inflammatory) to M2 (anti-inflammatory) [102], SOCS3, which had a low expression in arthritis [103], while TLR3 displayed low levels in inflammation and during viral infections [104]. Interestingly, Imatinib on the other hand also increased expression of some genes relevant for the antiviral response: CXCL16 [105], HAVCR2 [106], IFNG [107], RNASE2 and RNASE3 [108,109]. Finally, during Imatinib treatment, an increase in T cytotoxic and activated NK cells has been observed (Figure 2).

In conclusion, even if preliminary, our findings agree with data already published by Alves et al. that reported an increased number of NK cells and lower IL21 levels during treatment with TKIs and IFN [110], and support *the hypothesis that Imatinib might be a very good candidate to fight COVID-19 due to its anti-inflammatory action in a context of a conserved and efficient immunological infection control.*

4. CONCLUSIONS.

In Table 3 we resumed characteristics, pros and cons of drugs that, on the basis of above reported considerations, might be translated from the hematological scenario to the CoV-2 pandemic. Nevertheless, a further consideration has to be done about the costs of these possible new treatments: in 2018, a group of researchers from the Mayo Clinic performed a

cost/effectiveness analysis on 1047 patients treated for cGVHD. Among the drugs that can be used against COVID-19, in that study on cGVHD the cheapest resulted chloroquine (9,181 US$), followed by Imatinib (43,965 US$), and Ruxolitinib (97,807 US$) [111]. In our opinion, the final list of the "hematological" drugs that could represent promising options in the COVID-19 war might include also Ruxolitinib, Bosutinib, Imatinib and Begelomab. Ruxolitinib probably is the fastest and more powerful agent in the switching off the cytokine storm, as already shown in aGVHD and also in the first COVID-19 cases treated with this JAK1/2 inhibitor. Nevertheless, its doubtful safety from the infective point of view probably might impose at least the need of a careful observation of the immunocompetence in COVID-19 patients, also considering that super-infections have been documented in 8.5% of them. **TKIs** could be tried as further options: in different models of inflammations, Bosutinib showed optimal anti-inflammatory properties, already demonstrated by its ability of reverting the pro-inflammatory effects of Dasatinib. In addition, data coming from the experience in CML sustain its good safety profile and sustain the hypothesis of a rapid efficacy also. Imatinib displays a good anti-inflammatory effect, its use is characterized by a low infection rate; it is worth to remember also that Imatinib remain the cheapest drug and probably the TKI most frequently available worldwide. Begelomab, probably for a short period of time, might also be an interesting option for its capacity of destroying the strict negative link between Coronavirus and inflammation actors.

Thus, all considered, in a hypothetical "hematological-driven" algorithm (see graphical abstract), we could imagine using Begelomab for blocking the first steps of infection, Ruxolitinib to rapidly switch off the cytokine storm in the severe/hyperacute phase, and, then to sustain immunity (that Ruxolitinib is not able to do) and the required long-term anti-inflammatory effect by TKIs. On the other hand, the combination of Ruxolitinib with Nilotinib has already been adopted in a phase-I study in CML patients with unsatisfactory molecular response, without significant infections occurrence [112]. In the last few weeks many trials with some of the above mentioned drugs started and will gave us soon fundamental information; indeed, the war against SARS-CoV-2 has to be continued: rethinking drugs use with a multidisciplinary approach could be a possible improvement for the final victory.

CONFLICTS OF INTEREST

S. Galimberti, C. Baratè and M. Petrini were speakers in the events supported by Novartis, Pfizer, Celgene/BMS, Janssen, Roche, Incyte and members of advisory boards for Novartis and Janssen; A. Di Paolo was a speaker for Medac GmbH, Novartis, Roche, Incyte, and was an advisory board member for Novartis; C. Baldini and F. Ferro do not have any conflict of interest.

REFERENCES

[1]. Nicastri E, D'Abramo A, Faggioni G, De Santis R, Mariano A, Lepore L, et al. Coronavirus disease (COVID-19) in a paucisymptomatic patient: epidemiological and clinical challenge in settings with limited community transmission, Italy, February 2020. Euro Surveill. 25(11) (2020). doi: 10.2807/1560-7917

[2]. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med. (2020) Mar 10. doi: 10.7326/M20-0504.

[3]. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA. Mar 3 (2020). doi: 10.1001/jama.2020.3204.

[4]. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. J Med Virol. (2020) Mar 5. doi: 10.1002/jmv.25748.

[5]. COVID-19 National Emergency Response Center, Epidemiology and Case Management Team, Korea Centers for Disease Control and Prevention. Early Epidemiological and Clinical Characteristics of 28 Cases of Coronavirus Disease in South Korea. Osong Public Health Res Perspect. Feb;11(1) (2020) 8-14. doi: 10.24171/j.phrp.2020.11.1.03.

[6]. Shi F, Yu Q, Huang W, Tan C. 2019 Novel Coronavirus (COVID-19) Pneumonia with Hemoptysis as the Initial Symptom: CT and Clinical Features. Korean J Radiol. (2020) Mar 13. doi: 10.3348/kjr.2020.0181.

[7]. Sarzi-Puttini P, Giorgi V, Sirotti S, Marotto D, Ardizzone S, Rizzardini G, et al. COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? Clin Exp Rheumatol. 38(2) (2020) 337-342. Epub 2020 Mar 22.

[8]. Duan YJ, Liu Q, Zhao SQ, Huang F, Ren L, Liu L, Zhou YW. The Trial of Chloroquine in the Treatment of Corona Virus Disease 2019 （COVID-19） and Its Research Progress in Forensic Toxicology. Fa Yi Xue Za Zhi. 36(2) (2020). doi: 10.12116/j.issn.1004-5619.2020.02.001.

[9]. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Morgane Maihle et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. (2020) Mar 20:105949. doi: 10.1016/j.ijantimicag.2020.105949.

[10]. Scott LJ. Tocilizumab: A Review in Rheumatoid Arthritis. Drugs. 77(17) (2017) 1865-1879. doi: 10.1007/s40265-017-0829-7.

[11]. Biggioggero M, Crotti C, Becciolini A, Favalli EG. Tocilizumab in the treatment of rheumatoid arthritis: an evidence-based review and patient selection. Drug Des Devel Ther. 13 (2018) 57-70. doi: 10.2147/DDDT.S150580.

[12]. Hay KA. Cytokine release syndrome and neurotoxicity after CD19 chimeric antigen receptor-modified (CAR-) T cell therapy. Br J Haematol. 183(3) (2018) 364-374. doi: 10.1111/bjh.15644.

[13]. Kotch C, Barrett D, Teachey DT. Tocilizumab for the treatment of chimeric antigen receptor T cell-induced cytokine release syndrome. Expert Rev Clin Immunol. (8) (2019) 813-822. doi: 10.1080/1744666X.2019.1629904.

[14]. Ferro F, Elefante E, Baldini C, Bartoloni E, Puxeddu I, Talarico R, et al. COVID-19: the new challenge for rheumatologists. Clin Exp Rheumatol. 38(2) (2020) 175-180.

[15]. Lind-Holst M, Hartling UB, Christensen AE. High-dose anakinra as treatment for macrophage activation syndrome caused by refractory Kawasaki disease in an infant. BMJ Case Rep.12(8) (2019). pii: e229708. doi: 10.1136/bcr-2019-229708.

[16]. Al-Salama ZT, Scott LJ. Baricitinib: A Review in Rheumatoid Arthritis. Drugs. 78(7) (2018) 761-772. doi: 10.1007/s40265-018-0908-4.

[17]. Blauvelt A, Shi N, Burge R, Malatestinic WN, Lin CY, Lew CR, et al. Comparison of Real-World Treatment Patterns Among Psoriasis Patients Treated with Ixekizumab or Adalimumab. Patient Prefer Adherence. 14 (2020) 517-527. doi: 10.2147/PPA.S233993.

[18]. Ono T, Iwasaki T, Terada Y, Abe K, Lee J, Mochizuki M, Miyata K. Serum KL-6 elevation in a uveitis patient with Behçet's disease treated with adalimumab. Am J Ophthalmol Case Rep. 18 (2020) 100660. doi: 10.1016/j.ajoc.2020.100660.

[19]. Bersanelli M. Controversies about COVID-19 and anticancer treatment with immune checkpoint inhibitors. Immunotherapy. (2020) Mar 26. doi: 10.2217/imt-2020-0067.

[20]. Nassereddine S, Rafei H, Elbahesh E, Tabbara I. Acute Graft Versus Host Disease: A Comprehensive Review. Anticancer Res. 37(4) (2017)1547-1555.

[21]. Kerep AZ, Broome J, Pirsl F, Curtis LM, Steinberg SM, Mitchell SA, et al. Impact of the 2014 NIH chronic graft-versus-host disease scoring criteria modifications assessed in a large cohort of severely affected patients. Bone Marrow Transplant. 54(1) (2019) 76-84. doi: 10.1038/s41409-018-0224-3.

[22]. MacDonald KP, Blazar BR, Hill GR. Cytokine mediators of chronic graft-versus-host disease. J Clin Invest. 127(7) (2017) 2452-2463. doi: 10.1172/JCI90593.

[23]. McManigle W, Youssef A, Sarantopoulos S. B cells in chronic graft-versus-host disease. Hum Immunol. 80(6) (2019) 393-399. doi: 10.1016/j.humimm.2019.03.003.

[24]. Schulert GS, Grom AA. Pathogenesis of macrophage activation syndrome and potential for cytokine- directed therapies. Annu Rev Med. 66 (2015) 145-59. doi: 10.1146/annurev-med-061813-012806.

[25]. Moradinejad MH, Ziaee V. The incidence of macrophage activation syndrome in children with rheumatic disorders. Minerva Pediatr. 63(6) (2011) 459-66.

[26]. Yildiz H, Van Den Neste E, Defour JP, Danse E, Yombi JC. Adult haemophagocytic lymphohistiocytosis: a Review. QJM (2020) Jan 14. pii: hcaa011. doi: 10.1093/qjmed/hcaa011.

[27]. Grom AA, Horne A, De Benedetti F. Macrophage activation syndrome in the era of biologic therapy. Nat Rev Rheumatol. 12(5) (2016) 259-68. doi: 10.1038/nrrheum.2015.179.

[28]. Nassereddine S, Rafei H, Elbahesh E, Tabbara I. Acute Graft Versus Host Disease: A Comprehensive Review. Anticancer Res. 37(4) (2017) 1547-1555.

[29]. Sarantopoulos S, Cardones AR, Sullivan KM. How I treat refractory chronic graft-versus-host disease. Blood. 133(11) (2019) 1191-1200. doi: 10.1182/blood-2018-04-785899.

[30]. Kattner AS, Holler E, Holler B, Klobuch S, Weber D, Martinovic D, et al. IL6-receptor antibody tocilizumab as salvage therapy in severe chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation: a retrospective analysis. Ann Hematol. 99(4) (2020) 847-853. doi: 10.1007/s00277-020-03968-w.

[31]. Zaja F, Bacigalupo A, Patriarca F, Stanzani M, Van Lint MT, Filì C, et al. Treatment of refractory chronic GVHD with rituximab: a GITMO study. Bone Marrow Transplant. 40(3) (2007) 273-7.

[32]. Kharfan-Dabaja MA, Mhaskar AR, Djulbegovic B, Cutler C, Mohty M, Kumar A. Efficacy of rituximab in the setting of steroid-refractory chronic graft-versus-host disease: a systematic review and meta-analysis. Biol Blood Marrow Transplant. 15(9) (2009)1005-13. doi: 10.1016/j.bbmt.2009.04.003.

[33]. Bacigalupo A, Angelucci E, Raiola AM, Varaldo R, Di Grazia C, Gualandi F, et al. Treatment of steroid resistant acute graft versus host disease with an anti-CD26 monoclonal antibody-Begelomab. Bone Marrow Transplant. (2020) Mar 13. doi: 10.1038/s41409-020-0855-z.

[34]. Vankadari N, Wilce JA. Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. Emerg Microbes Infect. 9(1) (2020) 601-604. doi: 10.1080/22221751.2020.173956

[35]. Deretic V, Levine B. Autophagy balances inflammation in innate immunity. Autophagy. 14(2) (2018) 243-251. doi: 10.1080/15548627.2017.1402992

[36]. Drucker DJ. Coronavirus infections and type 2 diabetes-shared pathways with therapeutic implications. Endocr Rev. Apr 15. (2020) pii: bnaa011. doi: 10.1210/endrev/bnaa011

[37]. Iacobellis G. COVID-19 and diabetes: Can DPP4 inhibition play a role? Diabetes Res Clin Pract. (2020) 162:108125. doi: 10.1016/j.diabres.2020.108125

[38]. Miklos D, Cutler CS, Arora M, Waller EK, Jagasia M, Pusic I, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. Blood. 130(21) (2017) 2243-2250. doi: 10.1182/blood-2017-07-793786

[39]. Ernst M, Inglese M, Scholz GM, Harder KW, Clay FJ, Bozinovski S, et al. Constitutive activation of the SRC family kinase Hck results in spontaneous pulmonary inflammation and an enhanced innate immune response. J Exp Med. 196(5) (2002) 589-604. PMID:12208875

[40]. Waller EK, Miklos D, Cutler C, Arora M, Jagasia MH, Pusic I, et al. Ibrutinib for Chronic Graft-versus-Host Disease After Failure of Prior Therapy: 1-Year Update of a Phase 1b/2 Study. Biol Blood Marrow Transplant. 25(10) (2019) 2002-2007. doi: 10.1016/j.bbmt.2019.06.023.

[41]. King-Kallimanis BL, Wroblewski T, Kwitkowski V, De Claro RA, Gwise T, Bhatnagar V, et al. FDA review summary of patient-reported outcome results for ibrutinib in the treatment of chronic graft versus host disease. Qual Life Res. (2020) Feb 25. doi: 10.1007/s11136-020-02448-y.

[42]. Varughese T, Taur Y, Cohen N, Palomba ML, Seo SK, Hohl TM, Redelman-Sidi G. Serious Infections in Patients Receiving Ibrutinib for Treatment of Lymphoid Cancer. Clin Infect Dis. 67(5) (2018) 687-692. doi: 10.1093/cid/ciy175.

[43]. Treon SP, Castillo J, Skarbnik AP, Soumerai JD, Ghobrial IM, Guerrera ML, et al. The BTK-inhibitor ibrutinib may protect against pulmonary injury in COVID-19 infected patients. Blood. Apr 17. (2020) pii: blood.2020006288. doi: 10.1182/blood.2020006288.

[44]. Verstovsek S, Gotlib J, Mesa RA, Vannucchi AM, Kiladjian JJ, Cervantes F, et al. Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and -II pooled analyses. J Hematol Oncol. 10(1) (2017) 156. doi: 10.1186/s13045-017-0527-7.

[45]. Albeituni S, Verbist KC, Tedrick PE, Tillman H, Picarsic J, Bassett R, Nichols KE. Mechanisms of action of ruxolitinib in murine models of hemophagocytic lymphohistiocytosis. Blood. 134(2) (2019) 147-159. doi: 10.1182/blood.2019000761.

[46]. Jagasia M, Perales MA, Schroeder MA, Ali H, Shah NN, Chen YB, et al. Ruxolitinib for the treatment of steroid-refractory acute GVHD (REACH1): a multicenter, open-label, phase 2 trial. Blood. (2020) Mar 5. pii: blood.2020004823. doi: 10.1182/blood.2020004823.

[47]. Hui L, Qi L, Guoyu H, Xuliang S, Meiao T. Ruxolitinib for treatment of steroid-refractory graft-versus-host disease in adults: a systematic review and meta-analysis. Expert Rev Hematol. (2020) 1-11. doi: 10.1080/17474086.2020.1738214

[48]. Zeiser R, Burchert A, Lengerke C, Verbeek M, Maas-Bauer K, Metzelder SK, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. Leukemia. 29(10) (2015) 2062-8. doi: 10.1038/leu.2015.212.

[49]. Hui L, Qi L, Guoyu H, Xuliang S, Meiao T. Ruxolitinib for treatment of steroid-refractory graft-versus-host disease in adults: a systematic review and meta-analysis. Expert Rev Hematol. (2020) 1-11. doi: 10.1080/17474086.2020.1738214.

[50]. Caocci G, Murgia F, Podda L, Solinas A, Atzeni S, La Nasa G. Reactivation of hepatitis B virus infection following ruxolitinib treatment in a patient with myelofibrosis. Leukemia. 28(1) (2014) 225-7. doi: 10.1038/leu.2013.235.

[51]. Khalid F, Damlaj M, AlZahrani M, Abuelgasim KA, Gmati GE. Reactivation of tuberculosis following ruxolitinib therapy for primary myelofibrosis: Case series and literature review. Hematol Oncol Stem Cell Ther. (2020) Mar 16. pii: S1658-3876(20)30032-7. doi: 10.1016/j.hemonc.2020.02.003.

[52]. Lee SC, Feenstra J, Georghiou PR. Pneumocystis jiroveci pneumonitis complicating ruxolitinib therapy. BMJ Case Rep. (2014) Jun 2;2014. pii: bcr2014204950. doi: 10.1136/bcr-2014-204950.

[53]. Jain P, Kantarjian H, Cortes J. Chronic myeloid leukemia: overview of new agents and comparative analysis. Curr Treat Options Oncol. 14(2) (2013) 127-43. doi: 10.1007/s11864-013-0234-8.

[54]. Fava C, Rege-Cambrin G, Dogliotti I, Cerrano M, Berchialla P, Dragani M, et al. Observational study of chronic myeloid leukemia Italian patients who discontinued tyrosine kinase inhibitors in clinical practice. Haematologica. 20104(8) (2019) 1589-1596. doi: 10.3324/haematol.2018.205054.

[55]. Dumas PY, Bérard E, Bréal C, Dulucq S, Réa D, Nicolini F, et al. Killer immunoglobulin-like receptor genotypes and chronic myeloid leukemia outcomes after imatinib cessation for treatment-free remission. Cancer Med. 8(11) (2019) 4976-4985. doi: 10.1002/cam4.2371.

[56]. Caocci G, Martino B, Greco M, Abruzzese E, Trawinska MM, Lai S, et al. Killer immunoglobulin-like receptors can predict TKI treatment-free remission in chronic myeloid leukemia patients. Exp Hematol. 43(12) (2015) 1015-1018.e1. doi: 10.1016/j.exphem.2015.08.004.

[57]. Hughes A, Yong ASM. Immune Effector Recovery in Chronic Myeloid Leukemia and Treatment-Free Remission. Front Immunol. 8 (2017) 469. doi: 10.3389/fimmu.2017.00469.

[58]. Alsuliman T, Magro L, Coiteux V, Gauthier J, Srour M, Lionet A, et al. The concurrent administration of imatinib with extracorporeal photopheresis leads to complete and durable responses in patients with refractory sclerotic type chronic graft-versus-host disease. Curr Res Transl Med. (2019) Oct 17. pii: S2452-3186(19)30041-8. doi: 10.1016/j.retram.2019.10.001.

[59]. Olivieri A, Locatelli F, Zecca M, Sanna A, Cimminiello M, Raimondi R. et al. Imatinib for refractory chronic graft-versus-host disease with fibrotic features. Blood. 114(3) (2009) 709-18. doi: 10.1182/blood-2009-02-204156.

[60]. Sánchez-Ortega I, Parody R, Servitje O, Muniesa C, Arnan M, Patino B, et al. Imatinib and dasatinib as salvage therapy for sclerotic chronic graft-vs-host disease. Croat Med J. 57(3) (2016) 247-54.

[61]. Iurlo A, Galimberti S, Abruzzese E, Annunziata M, Bonifacio M, Latagliata R, et al. Pleural effusion and molecular response in dasatinib-treated chronic myeloid leukemia patients in a real-life Italian multicenter series. Ann Hematol. 97(1) (2018) 95-100. doi: 10.1007/s00277-017-3144-1.

[62]. Bergeron A, Réa D, Levy V, Picard C, Meignin V, Tamburini J, et al. Lung abnormalities after dasatinib treatment for chronic myeloid leukemia: a case series. Am J Respir Crit Care Med. 176(8) (2007) 814-8.

[63]. de Lavallade H, Punnialingam S, Milojkovic D, Bua M, Khorashad JS, Gabriel IH, et al. Pleural effusions in patients with chronic myeloid leukaemia treated with dasatinib may have an immune-mediated pathogenesis. Br J Haematol. 141(5) (2008) 745-7. doi: 10.1111/j.1365-2141.2008.07108.x.

[64]. Maiti A, Cortes JE, Patel KP, Masarova L, Borthakur G, Ravandi F, et al. Long-term results of frontline dasatinib in chronic myeloid leukemia. Cancer. 126(7) (2020) 1502-1511. doi: 10.1002/cncr.32627.

[65]. Cortes JE, Saglio G, Kantarjian HM, Baccarani M, Mayer J, Boqué C, et al. Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial. J Clin Oncol. 34(20) (2016) 2333-40. doi: 10.1200/JCO.2015.64.8899.

[66]. Isfort S, Crysandt M, Gezer D, Koschmieder S, Brümmendorf TH, Wolf D. Bosutinib: A Potent Second-Generation Tyrosine Kinase Inhibitor. Recent Results Cancer Res. 212 (2018) 87-108. doi: 10.1007/978-3-319-91439-8_4.

[67]. Tiribelli M, Abruzzese E, Capodanno I, Sorà F, Trabacchi E, Iurlo A, et al. Efficacy and safety of bosutinib in chronic phase CML patients developing pleural effusion under dasatinib therapy. Ann Hematol. 98(11) (2019) 2609-2611. doi: 10.1007/s00277-019-03802-y.

[68]. Zhang C, Leng L, Li Z, Zhao Y, Jiao J. Identification of biomarkers and drug repurposing candidates based on an immune-, inflammation- and membranous glomerulonephritis-associated triplets network for membranous glomerulonephritis. BMC Med Genomics. 13(1) (2020) 5. doi: 10.1186/s12920-019-0655-8.

[69]. Ma L, Manaenko A, Ou YB, Shao AW, Yang SX, Zhang JH. Bosutinib Attenuates Inflammation via Inhibiting Salt-Inducible Kinases in Experimental Model of Intracerebral Hemorrhage on Mice. Stroke. 48(11) (2017) 3108-3116. doi: 10.1161/STROKEAHA.117.017681.

[70]. Lonskaya I, Hebron ML, Selby ST, Turner RS, Moussa CE. Nilotinib and bosutinib modulate pre-plaque alterations of blood immune markers and neuro-inflammation in Alzheimer's disease models. Neuroscience. 304 (2015) 316-27. doi: 10.1016/j.neuroscience.2015.07.070.

[71]. Cortes JE, Gambacorti-Passerini C, Deininger MW, Mauro MJ, Chuah C, Kim DW, et al. Bosutinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia: Results From the Randomized BFORE Trial. J Clin Oncol. 36(3) (2018) 231-237. doi: 10.1200/JCO.2017.74.7162.

[72]. Sacha T, Saglio G. Nilotinib in the treatment of chronic myeloid leukemia. Future Oncol. 15(9) (2019) 953-965. doi: 10.2217/fon-2018-0468.

[73]. Marinelli Busilacchi E, Costantini A, Viola N, Costantini B, Olivieri J, Butini L, et al. Immunomodulatory Effects of Tyrosine Kinase Inhibitor In Vitro and In Vivo Study. Biol Blood Marrow Transplant. 24(2) (2018) 267-275. doi: 10.1016/j.bbmt.2017.10.039.

[74]. Marinelli Busilacchi E, Costantini A, Mancini G, Tossetta G, Olivieri J, Poloni A, et al. Nilotinib Treatment of Patients Affected by Chronic Graft-versus-Host Disease Reduces Collagen Production and Skin Fibrosis by Downmodulating the TGF-β and p-SMAD Pathway. Biol Blood Marrow Transplant. (2020) Jan 30. pii: S1083-8791(20)30046-X. doi: 10.1016/j.bbmt.2020.01.014.

[75]. Hochhaus A, Saglio G, Hughes TP, Larson RA, Kim DW, Issaragrisil S, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia. 30(5) (2016) 1044-54. doi: 10.1038/leu.2016.5.

[76]. Caocci G, Mulas O, Annunziata M, Luciano L, Abruzzese E, Bonifacio Met al. Long-term mortality rate for cardiovascular disease in 656 chronic myeloid leukaemia patients treated with second- and third-generation tyrosine kinase inhibitors. Int J Cardiol. 301 (2020) 163-166. doi: 10.1016/j.ijcard.2019.10.036.

[77]. Caocci G, Mulas O, Annunziata M, Luciano L, Bonifacio M, Orlandi EM, et al. Cardiovascular toxicity in patients with chronic myeloid leukemia treated with second-generation tyrosine kinase inhibitors in the real-life practice: Identification of risk factors and the role of prophylaxis. Am J Hematol. 93(7) (2018) E159-E161. doi: 10.1002/ajh.25102.

[78]. Bocchia M, Galimberti S, Aprile L, Sicuranza A, Gozzini A, Santilli F, et al. Genetic predisposition and induced pro-inflammatory/pro-oxidative status may play a role in increased atherothrombotic events in nilotinib treated chronic myeloid leukemia patients. Oncotarget. 7(44) (2016) 72311-72321. doi: 10.18632/oncotarget.11100.

[79]. Gale RP, Hehlmann R, Zhang MJ, Hasford J, Goldman JM, Heimpel H, et al. Survival with bone marrow transplantation versus hydroxyurea or interferon for chronic myelogenous leukemia. The German CML Study Group. Blood. 91(5) (1998) 1810-9.

[80]. Hasselbalch HC, Holmström MO. Perspectives on interferon-alpha in the treatment of polycythemia vera and related myeloproliferative neoplasms: minimal residual disease and cure? Semin Immunopathol. 41(1) (2019) 5-19. doi: 10.1007/s00281-018-0700-2]

[81]. Thompson PA, Ravandi F. How I manage patients with hairy cell leukaemia.Br J Haematol. 177(4) (2017) 543-556. doi: 10.1111/bjh.14524]

[82]. Smyth L, Buckstein R, Pennell N, Weerasinghe R, Cheung MC, Imrie K, et al. Autologous stem cell transplant and combination immunotherapy of rituximab and interferon-α induces prolonged clinical and molecular remissions in patients with follicular lymphoma. Br J Haematol. 184(3) (2019) 469-472. doi: 10.1111/bjh.15118.

[83]. Joshua DE, MacCallum S, Gibson J. Role of alpha interferon in multiple myeloma. Blood Rev. 11(4) (1997) 191-200. PMID: 9481449].

[84]. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med. 3(9) (2006) e343. PMID:16968120].

[85]. Raanani P, Ben-Bassat I. Immune-mediated complications during interferon therapy in hematological patients. Acta Haematol. 107(3) (2002) 133-44. PMID:11978934.

[86]. Prokunina-Olsson L, Alphonse N, Dickenson RE, Durbin JE, Glenn JS, Hartmann R, et al. COVID-19 and emerging viral infections: The case for interferon lambda. J Exp Med. 217(5) (2020) pii: e20200653. doi: 10.1084/jem.20200653].

[87]. Cai W LA, Galtung HK, Guerreiro EM, Øvstebø R, Thiede B, Utheim TP, et al.. Proteomic and histopathological characterisation of sicca subjects and primary Sjögren's syndrome patients reveals promising tear, saliva and extracellular vesicle disease biomarkers. Arthritis Res Ther. 21(1) (2019) 181. doi: 10.1186/s13075-019-1961-4.

[88]. Li N, Shi RH. lncRNACNN3-206 activates intestinal epithelial cell apoptosis and invasion by sponging miR-212, an implication for Crohn's disease. World J Gastroenterol. 26(5) (2020) 478-498. doi: 10.3748/wjg.v26.i5.478.

[89]. Ribon M, Mussard J, Semerano L, Singer BB, Decker P. Extracellular Chromatin Triggers Release of Soluble CEACAM8 Upon Activation of Neutrophils. Front Immunol. 10 (2019) 1346. doi: 10.3389/fimmu.2019.01346.

[90]. Trzybulska D, Olewicz-Gawlik A, Graniczna K, Kisiel K, Moskal M, Cieślak D, et al. Quantitative analysis of elastase and cathepsin G mRNA levels in peripheral blood CD14(+) cells from patients with rheumatoid arthritis. Cell Immunol. 292(1-2) (2014) 40-4. doi: 10.1016/j.cellimm.2014.08.009.

[91]. Bao J, Chen Z, Xu L, Wu L, Xiong Y. Rapamycin protects chondrocytes against IL-18-induced apoptosis and ameliorates rat osteoarthritis. Aging (Albany NY). (2020) Mar 17;12. doi: 10.18632/aging.102937.

[92]. Sung PS, Chang WC, Hsieh SL. CLEC5A: A Promiscuous Pattern Recognition Receptor to Microbes and Beyond. Adv Exp Med Biol. 1204 (2020) 57-73. doi: 10.1007/978-981-15-1580-4_3.

[93]. Cattaneo A, Cattaneo N, Galluzzi S, Provasi S, Lopizzo N, et al; INDIA-FBP Group. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging. 49 (2017) 60-68. doi: 10.1016/j.neurobiolaging.2016.08.019.

[94]. Marschallinger J, Iram T, Zardeneta M, Lee SE, Lehallier B, Haney MS, et al. Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. Nat Neurosci. 23(2) (2020) 194-208. doi: 10.1038/s41593-019-0566-1.

[95]. Hruska P, Kuruczova D, Vasku V, Bienertova-Vasku J. MiR-21 binding site SNP within ITGAM associated with psoriasis susceptibility in women. PLoS One. 14(6) (2019) e0218323. doi: 10.1371/journal.pone.0218323.

[96]. Silbereisen A, Hallak AK, Nascimento GG, Sorsa T, Belibasakis GN, Lopez R, Bostanci N. Regulation of PGLYRP1 and TREM-1 during Progression and Resolution of Gingival Inflammation. JDR Clin Trans Res. 4(4) (2019) 352-359. doi: 10.1177/2380084419844937.

[97]. Cai W, Dai X, Chen J, Zhao J, Xu M, Zhang L, Yang B, et al. STAT6/Arg1 promotes microglia/macrophage efferocytosis and inflammation resolution in stroke mice. JCI Insight. 4(20). (2019) pii: 131355. doi: 10.1172/jci.insight.131355.

[98]. Brennan FH, Jogia T, Gillespie ER, Blomster LV, Li XX, Nowlan B, et al. Complement receptor C3aR1 controls neutrophil mobilization following spinal cord injury through physiological antagonism of CXCR2. JCI Insight. 4(9) (2019). pii: 98254. doi: 10.1172/jci.insight.98254.

[99]. Nagaishi T, Pao L, Lin SH, Iijima H, Kaser A, Qiao SW, et al. SHP1 phosphatase-dependent T cell inhibition by CEACAM1 adhesion molecule isoforms. Immunity. 25(5) (2006) 769-81.

[100]. Wątek M, Wnorowska U, Wollny T, Durnaś B, Wolak P, Kościołek-Zgódka S, et al. Hypogelsolinemia in Patients Diagnosed with Acute Myeloid Leukemia at Initial Stage of Sepsis. Med Sci Monit. 25 (2019) 1452-1458. doi: 10.12659/MSM.911904.

[101]. Slade JA, Hall JV, Kintner J, Phillips-Campbell R, Schoborg RV. Host Nectin-1 Promotes Chlamydial Infection in the Female Mouse Genital Tract, but Is Not Required for Infection in a Novel Male Murine Rectal Infection Model. PLoS One. 11(8) (2016) e0160511. doi: 10.1371/journal.pone.0160511.

[102]. Quero L, Tiaden AN, Hanser E, Roux J, Laski A, Hall J, Kyburz D. miR-221-3p Drives the Shift of M2-Macrophages to a Pro-Inflammatory Function by Suppressing JAK3/STAT3 Activation. Front Immunol. 10 (2020) 3087. doi: 10.3389/fimmu.2019.03087.

[103]. Gui T, He BS, Gan Q, Yang C. Enhanced SOCS3 in osteoarthiritis may limit both proliferation and inflammation. Biotech Histochem. 92(2) (2017) 107-114. doi: 10.1080/10520295.2017.1278792.

[104]. Ribes S, Arcilla C, Ott M, Schütze S, Hanisch UK, Nessler S, Nau R. Pre-treatment with the viral Toll-like receptor 3 agonist poly(I:C) modulates innate immunity and protects neutropenic mice infected intracerebrally with Escherichia coli. J Neuroinflammation. 17(1) (2020) 24. doi: 10.1186/s12974-020-1700-4.

[105]. Touzelet O, Broadbent L, Armstrong SD, Aljabr W, Cloutman-Green E, Power UF, Hiscox JA. The secretome profiling of a pediatric airway epithelium infected with hRSV identified aberrant apical/basolateral trafficking and novel immune modulating (CXCL6, CXCL16, CSF3) and antiviral (CEACAM1) proteins. Mol Cell Proteomics. (2020) Feb 19. pii: mcp.RA119.001546. doi: 10.1074/mcp.RA119.001546.

[106]. Liong S, Lim R, Barker G, Lappas M. Hepatitis A virus cellular receptor 2 (HAVCR2) is decreased with viral infection and regulates pro-labour mediators OA. Am J Reprod Immunol. 78(1) (2017). doi: 10.1111/aji.12696.

[107]. Gao P, Fan L, Du H, Xiang B, Li Y , Sun M, et al. Recombinant Duck Interferon Gamma Inhibits H5N1 Influenza Virus Replication In Vitro and In Vivo. J Interferon Cytokine Res. 38(7) (2018) 290-297. doi: 10.1089/jir.2018.0034.

[108]. Rosenberg HF. Eosinophil-Derived Neurotoxin (EDN/RNase 2) and the Mouse Eosinophil-Associated RNases (mEars): Expanding Roles in Promoting Host Defense. Int J Mol Sci. 16(7) (2015) 15442-55. doi: 10.3390/ijms160715442.

[109]. Cao L, Wu XM, Nie P, Chang MX. The negative regulation of piscine CD44c in viral and bacterial infection. Dev Comp Immunol. 96 (2019) 135-143. doi: 10.1016/j.dci.2019.03.005.

[110]. Alves R, McArdle SEB, Vadakekolathu J, Gonçalves AC, Freitas-Tavares P, Pereira A, et al. Flow cytometry and targeted immune transcriptomics identify distinct profiles in patients with chronic myeloid leukemia receiving tyrosine kinase inhibitors with or without interferon-α. J Transl Med. 18(1) (2020) 2. doi: 10.1186/s12967-019-02194-x.

[111]. Yalniz FF, Murad MH, Lee SJ, Pavletic SZ, Khera N, Shah ND, Hashmi SK. Steroid Refractory Chronic Graft-Versus-Host Disease: Cost-Effectiveness Analysis. Biol Blood Marrow Transplant. 24(9) (2018) 1920-1927. doi: 10.1016/j.bbmt.2018.03.008.

[112]. Sweet K, Hazlehurst L, Sahakian E, Powers J, Nodzon L, Kayali F, Hyland K et al. A phase I clinical trial of ruxolitinib in combination with nilotinib in chronic myeloid leukemia patients with molecular evidence of disease. Leuk Res. 74 (2018) 89-96. doi: 10.1016/j.leukres.2018.10.002.

[113]. Cheng Y, Pereira M, Raukar NP, Reagan JL, Quesenberry M, Goldberg L, et al. Inflammation-related gene expression profiles of salivary extracellular vesicles in patients with head trauma. Neural Regen Res. 15(4) (2020) 676-681. doi: 10.4103/1673-5374.266924.

[114]. Tsou YA, Tung YT, Wu TF, Chang GR, Chen HC, Lin CD, et al. Lactoferrin interacts with SPLUNC1 to attenuate lipopolysaccharide-induced inflammation of human nasal epithelial cells via down-regulated MEK1/2-MAPK signaling. Biochem Cell Biol. 95(3) (2017) 394-399. doi: 10.1139/bcb-2016-0047.

[115]. Yoon BH, Romero R, Park JY, Oh KJ, Lee J, Conde-Agudelo A, Hong JS. Antibiotic administration can eradicate intra-amniotic infection or intra-amniotic inflammation in a subset of patients with preterm labor and intact membranes. Am J Obstet Gynecol. 221(2) (2019) 142.e1-142.e22. doi: 10.1016/j.ajog.2019.03.018.

[116]. Funel N, Dini V, Janowska A, Loggini B, Minale M, Grieco F, et al. Triticum vulgare Extract Modulates Protein-Kinase B and Matrix Metalloproteinases 9 Protein Expression in BV-2 Cells: Bioactivity on Inflammatory Pathway Associated with Molecular Mechanism Wound Healing. Mediators Inflamm. 2020 (2020) 2851949. doi: 10.1155/2020/2851949.

[117]. Aratani Y. Myeloperoxidase: Its role for host defense, inflammation, and neutrophil function. Arch Biochem Biophys. 640 (2018) 47-52. doi: 10.1016/j.abb.2018.01.004.

[118]. Lara-Guzmán OJ, Gil-Izquierdo Á, Medina S, Osorio E, Álvarez-Quintero R, Zuluaga N, et al. Oxidized LDL triggers changes in oxidative stress and inflammatory biomarkers in human macrophages. Redox Biol. 15 (2018) 1-11. doi: 10.1016/j.redox.2017.11.017.

[119]. Shi Y, Zhang Z, Cai D, Kuang J, Jin S, Zhu C, et al. Urokinase Attenuates Pulmonary Thromboembolism in an Animal Model by Inhibition of Inflammatory Response. J Immunol Res. 2018 (2018) 6941368. doi: 10.1155/2018/6941368.

[120]. Yun Y, Kanda A, Kobayashi Y, Van Bui D, Suzuki K, Sawada S, et al. Increased CD69 expression on activated eosinophils in eosinophilic chronic rhinosinusitis correlates with clinical findings. Allergol Int. (2020) Jan 9. pii: S1323-8930(19)30194-7. doi: 10.1016/j.alit.2019.11.002.

[121]. Bottazzi B, Inforzato A, Messa M, Barbagallo M, Magrini E, Garlanda C, Mantovani A. The pentraxins PTX3 and SAP in innate immunity, regulation of inflammation and tissue remodelling. J Hepatol. 64(6) (2016) 1416-27. doi: 10.1016/j.jhep.2016.02.029.

[122]. Kitisin K, Ganesan N, Tang Y, Jogunoori W, Volpe EA, Kim SS, et al. Disruption of transforming growth factor-beta signaling through beta-spectrin ELF leads to hepatocellular cancer through cyclin D1 activation. Oncogene. 2007 26(50) (2007) 7103-10.

[123]. Isaac R, Goldstein I, Furth N, Zilber N, Streim S, Boura-Halfon S, et al.TM7SF3, a novel p53-regulated homeostatic factor, attenuates cellular stress and the subsequent induction of the unfolded protein response. Cell Death Differ. 24(1) (2017) 132-143. doi: 10.1038/cdd.2016.108.

[124]. Niture S, Moore J, Kumar D. TNFAIP8: Inflammation, Immunity and Human Diseases. J Cell Immunol. 1(2) (2019) 29-34.

[125]. Ostendorf T, Zillinger T, Andryka K, Schlee-Guimaraes TM, Schmitz S, Marx S, et al. Immune Sensing of Synthetic, Bacterial, and Protozoan RNA by Toll-like Receptor 8 Requires Coordinated Processing by RNase T2 and RNase 2. Immunity. 52(4) (2020) 591-605.e6. doi: 10.1016/j.immuni.2020.03.009.

[126]. Ratcliffe C, Wandschneider B, Baxendale S, Thompson P, Koepp MJ, Caciagli L. Cognitive Function in Genetic Generalized Epilepsies: Insights From Neuropsychology and Neuroimaging. Front Neurol. 11 (2020) 144. doi: 10.3389/fneur.2020.00144.

[127]. Merhi Z, Polotsky AJ, Bradford AP, Buyuk E, Chosich J, Phang T, et al. Adiposity Alters Genes Important in Inflammation and Cell Cycle Division in Human Cumulus Granulosa Cell. Reprod Sci. 22(10) (2015) 1220-8. doi: 10.1177/1933719115572484.

[128]. Krześniak M, Zajkowicz A, Gdowicz-Kłosok A, Głowala-Kosińska M, Łasut-Szyszka B, Rusin M. Synergistic activation of p53 by actinomycin D and nutlin-3a is associated with the upregulation of crucial regulators and effectors of innate immunity. Cell Signal. 69 (2020) 109552. doi: 10.1016/j.cellsig.2020.109552.

[129]. Kusuyama J, Komorizono A, Bandow K, Ohnishi T, Matsuguchi T. CXCL3 positively regulates adipogenic differentiation. J Lipid Res. 57(10) (2016) 806-1820.

[130]. Kröller-Schön S, Daiber A, Steven S, Oelze M, Frenis K, Kalinovic S, et al. Crucial role for Nox2 and sleep deprivation in aircraft noise-induced vascular and cerebral oxidative stress, inflammation, and gene regulation. Eur Heart J. 39(38) (2018) 3528-3539. doi: 10.1093/eurheartj/ehy333.

[131]. Hsu KL, Tsuboi K, Adibekian A, Pugh H, Masuda K, Cravatt BF. DAGLβ inhibition perturbs a lipid network involved in macrophage inflammatory responses. Nat Chem Biol. 8(12) (2012) 999-1007. doi: 10.1038/nchembio.1105.

[132]. Gu W, Wen D, Lu H, Zhang A, Wang H, Du J, et al. MiR-608 Exerts Anti-inflammatory Effects by Targeting ELANE in Monocytes. J Clin Immunol. 40(1) (2020)147-157. doi: 10.1007/s10875-019-00702-8.

[133]. Cardenas A, Sordillo JE, Rifas-Shiman SL, Chung W, Liang L, Coull BA, et al. The nasal methylome as a biomarker of asthma and airway inflammation in children. Nat Commun. 10(1) (2019) 3095. doi: 10.1038/s41467-019-11058-3.

[134]. Wang C, Ke Y, Liu S, Pan S, Liu Z, Zhang H, et al. Ectopic fibroblast growth factor receptor 1 promotes inflammation by promoting nuclear factor-κB signaling in prostate cancer cells. J Biol Chem. 293(38) (2018) 14839-14849. doi: 10.1074/jbc.RA118.002907.

[135]. Markic J, Jeroncic A, Polancec D, Bosnjak N, Markotic A, Mestrovic J, Culic VC. CD15s is a potential biomarker of serious bacterial infection in infants admitted to hospital. Eur J Pediatr. 172(10) (2013) 1363-9. doi: 10.1007/s00431-013-2047-y.

[136]. Li F, Sheng Y, Hou W, Sampath P, Byrd D, Thorne S, Zhang Y. CCL5-armed oncolytic virus augments CCR5-engineered NK cell infiltration and antitumor efficiency. J Immunother Cancer. 8(1) (2020). pii: e000131. doi: 10.1136/jitc-2019-000131.

[137]. Matsuo K, Nagakubo D, Komori Y, Fujisato S, Takeda N, Kitamatsu M, et al. CCR4 Is Critically Involved in Skin Allergic Inflammation of BALB/c Mice. J Invest Dermatol. 138(8) (2018) 1764-1773. doi: 10.1016/j.jid.2018.02.027.

[138]. Li F, Sheng Y, Hou W, Sampath P, Byrd D, Thorne S, Zhang Y. CCL5-armed oncolytic virus augments CCR5-engineered NK cell infiltration and antitumor efficiency. J Immunother Cancer. 8(1) (2020). pii: e000131. doi: 10.1136/jitc-2019-000131.

[139]. Hui E, Cheung J, Zhu J, Su X, Taylor MJ, Wallweber HA, et al. T cell costimulatory receptor CD28 is a primary target for PD-1-mediated inhibition. Science. 355(6332) (2017) 1428-1433. doi: 10.1126/science.aaf1292.

[140]. Wang ZQ, Milne K, Webb JR, Watson PH. CD74 and intratumoral immune response in breast cancer. Oncotarget. 8(8) (2017) 12664-12674. doi: 10.18632/oncotarget.8610.

[141]. Leonardi I, Li X, Semon A, Li D, Doron I, Putzel G, et al. CX3CR1^{+} mononuclear phagocytes control immunity to intestinal fungi. Science. 359(6372) (2018) 232-236. doi: 10.1126/science.aao1503.

[142]. Groom JR, Luster AD. CXCR3 in T cell function. Exp Cell Res. 317(5) (2011) 620-31. doi: 10.1016/j.yexcr.2010.12.017.

[143]. Bahal D, Hashem T, Nichols KE, Das R. SLAM-SAP-Fyn: Old Players with New Roles in iNKT Cell Development and Function. Int J Mol Sci. 20(19) (2019) pii: E4797. doi: 10.3390/ijms20194797.

[144]. Xu T, Keller A, Martinez GJ. NFAT1 and NFAT2 Differentially Regulate CTL Differentiation Upon Acute Viral Infection. Front Immunol. 10 (2019)184. doi: 10.3389/fimmu.2019.00184.

[145]. Lelubre C, Medfai H, Akl I, Leentjens J, Kox M, Pickkers P, et al. Leukocyte phosphodiesterase expression after lipopolysaccharide and during sepsis and its relationship with HLA-DR expression. J Leukoc Biol. 101(6) (2017) 1419-1426. doi: 10.1189/jlb.5A0516-240R

[146]. Mangan MS, Melo-Silva CR, Luu J, Bird CH, Koskinen A, Rizzitelli A, et al. A pro-survival role for the intracellular granzyme B inhibitor Serpinb9 in natural killer cells during poxvirus infection. Immunol Cell Biol. 2017 Nov;95(10):884-894. doi: 10.1038/icb.2017.59.

[147]. Li H, Fan C, Feng C, Wu Y, Lu H, He P, Yang Xet al. Inhibition of phosphodiesterase-4 attenuates murine ulcerative colitis through interference with mucosal immunity. Br J Pharmacol. 176(13) (2019) 2209-2226. doi: 10.1111/bph.14667.

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AUTHOR CONTRIBUTION.

S. Galimberti and C. Baldini wrote the manuscript; all authors revised and approved it.

CONFLICTS OF INTEREST.

S. Galimberti, C. Baratè and M. Petrini were speakers in the events supported by Novartis, Pfizer, Celgene/BMS, Janssen, Roche, Incyte and members of advisory boards for Novartis and Janssen; A. Di Paolo was a speaker for Medac GmbH, Novartis, Roche, Incyte, and was an advisory board member for Novartis; C. Baldini and F. Ferro do not have any conflict of interest.

Figure 1. CML: Volcano plots of some pathways de-regulated by 6 months of treatment with Imatinib.

Some of the up- (red squares) and down- (green squares) genes de-regulated during treatment of CML patients with Imatinib are represented by volcano plots. Statistical significance (at 0.05 and 0.01) are indicated with dotted and continuous lines, respectively. In a) the Antigen presentation pathway, in b) the Cytokines pathway, in c) the FCR signaling pathway is represented.

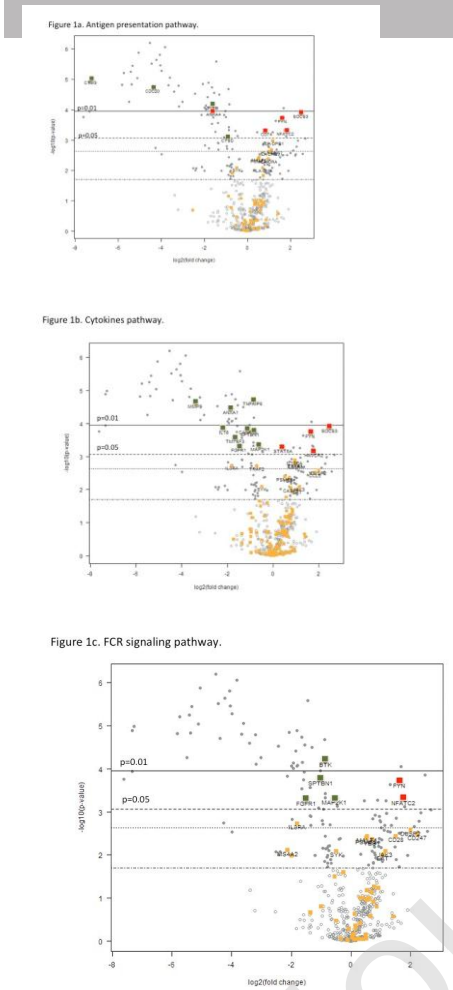

Figure 2. CML: Box plots representing some cellular types de-regulated by 6 months of treatment with Imatinib.

Changes of mRNAs identifying different cellular populations after Imatinib treatment are here reported. In a) cytotoxic cells (defined as GZMA+, NKG7+, CD94+), whose mRNAs resulted increased by Imatinib; in b) NK cells (CD56 bright), that increased after Imatinib treatment; in c) mast cells (defined as CPA3+, tryptase+, MSGA2+, CCL22+), whose RNAs were decreased by Imatinib; in d) RNAs characterizing neutrophils (defined as FPR1+, SIGLEC5+, CSF3R+, FCAR+), that remained unchanged in respect of diagnosis.

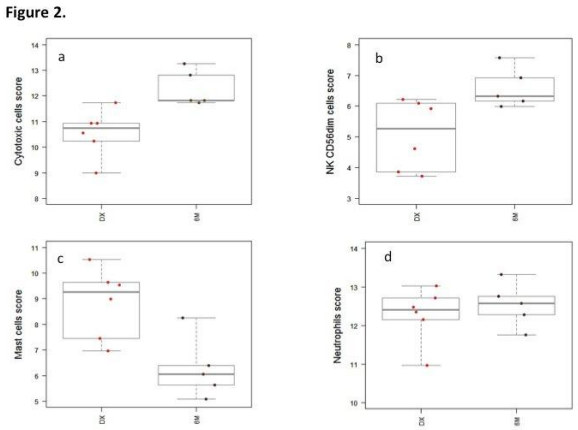

Figure 3. GRAPHICAL ABSTRACT

A possible therapeutic algorithm for COVID-19.

A possible “hematological-based” integrated algorithm for COVID-19 treatment, based on different disease phases, is here represented. In the early stage of SARS-CoV2 infection, chloroquine, imatinib or begelomab might be useful for blocking the attack of the viral S protein to the CD26 virus receptors, for modifying the lysosome pH or for restoring the anti-microbial autophagy. During an eventual mild COVID-19 phase, the anti-viral host reaction might be sustained by imatinib or ibrutinib, that at the same time might exert also an useful anti-inflammatory action, even if moderate. In the more severe phases of COVID-19, the anti-JAK1/2 inhibitors might be useful, alone or in combination with anti-cytokine monoclonal antibodies, such as Tocilizumab.

GRAPHICAL ABSTRACT

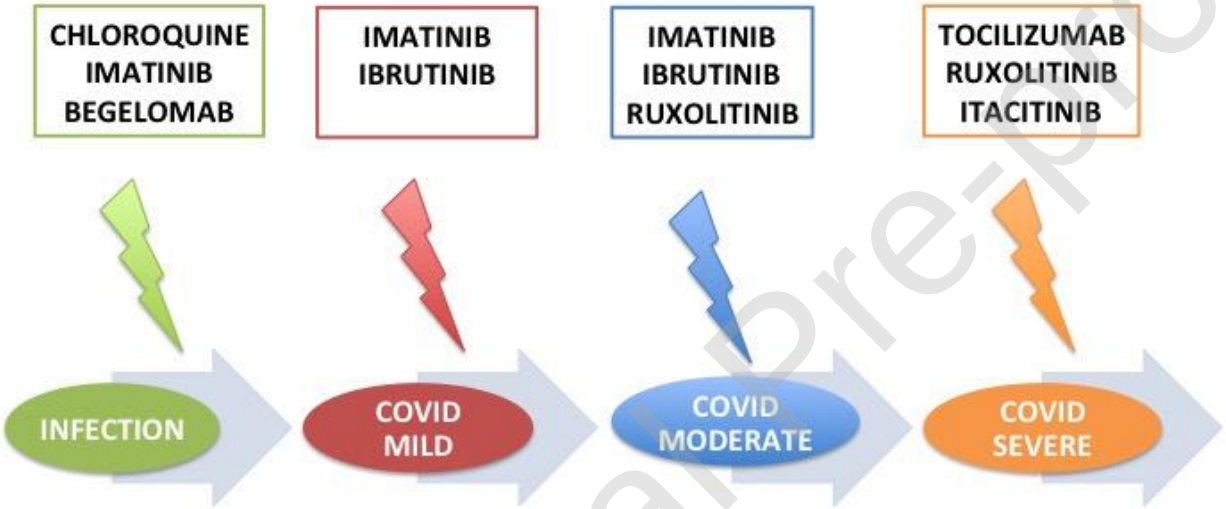

Table 1. CML gene expression profiling.

Table represents all genes that, among the 770 genes whose expression had been tested by the Nanostring “Human nCounter Myeloid Innate Immunity” panel, resulted up- (in red) and down- (in green) regulated after 6 months of treatment with Imatinib. The adopted Nanostring panel allows to classify genes in 19 different pathways. The Table reports for each gene its respective pathway of belonging.

Table 1.

GENE ID	PATHWAY
ANXA4	Ag present
ARG1	metabolism
BTK	BCR
C3AR1	complement
CAMP	pat respo
CASP10	cytokines
CDC20	Ag present
CEACAM1	migration
CEACAM8	migration
CLEC5A	ly activation
COL17A1	ECM
CTSG	Ag present
CXCL2	chemokines
CXCL3	chemokines
CYBB	Ag present
DAGLB	metabolism
ELANE	ECM
EPX	pat resp
FGFR1	cytokines
FUT4	metabolism

GENE ID	PATHWAY
GRN	pat resp
GSN	pat resp
IL18	cytokines
ITGAM	migration
LTA4H	metabolism
MAP2K1	angiogenesis
MMP8	ECM
MMP9	ECM
MPO	pat resp
NECTIN1	migration
OLR1	migration
PGLYRP1	pat resp
PLAU	complement
PRG2	pat resp
PTX3	pat resp
RNASE2	pat resp
RNASE3	pat resp
SPTBN1	cytokines
TM7SF3	cytokines
TNFAIP8	cytokines

Table 1.

GENE ID	PATHWAY
CCL5	chemokines
CCR4	chemokines
CCR5	chemokines
CD28	migration
CD74	Ag presentation
CX3CR1	chemokines
CXCL16	chemokines
CXCR3	chemokines
FYN	Ag presentation
HAVCR2	cytokines
IFNG	Ag presentation
JAK3	chemokines
NFATC2	Ag presentation
PDE4A	metabolism
SERPINB9	pat resp
SOCS3	Ag presentation
STAT5A	cytokines
TLR3	pat resp

Table 2. CML gene expression profiling.

Table represents all genes that resulted Up- (in red) and down- (in green) regulated after 6 months of treatment with Imatinib, as listed in Table 1. Table 2 in addition for each gene reports the respective physiological function (with correspondent literature references) and the final effect resulting from mRNA de-regulation made by 6 months of Imatinib, with focus on the inflammation and on the immunological infection control.

Table 2.

GENE ID	function	output on inflammation/ immune resp	ref
ANXA4	high in Sjogren	anti infl	87
ARG1	immunosuppressive	pro immun	97
BTK	sustains GVHD	anti infl	38
C3AR1	neutrophils chemotaxis antagonist	pro immun	98
CAMP	increased in inflammation	anti infl	126
CASP10	increased in Chron	anti infl	88
CDC20	increased in the adiposity inflamm model	anti infl	127
CEACAM1	inhibits T lynf	pro immun	99
CEACAM8	high in arthritis	anti infl	89
CLEC5A	high in neurogen shock	anti infl	92
COL17A1	induce IL7 that sustains T & B lynf	anti immun	128
CTSG	high in rheumatic arthritis	anti infl	90
CXCL2	high in Alzheimer	anti infl	70
CXCL3	sustain adipogenesis	anti infl	129
CYBB	increased in inflammation	anti infl	130
DAGLB	sustains production of arachidonic acid	anti infl	131

ELANE	high in LPS inflammation	anti infl	132
EPX	high in asthma	anti infl	133
FGFR1	high in prostatic inflammation	anti infl	134
FUT4	increased in bacterial infections	anti infl	135

Table 2.

GENE ID	function	output on inflammation	ref
GRN	high in dementhia	anti	94
GSN	increases NK apoptosis	pro immun	100
IL18	high in arthritis	anti	91
ITGAM	high in psoriasis	anti	95
LTA4H	high after trauma	anti	113
MAP2K1	high in sinusitis	anti	114
MMP8	high in intra-amniotic infections	anti	115
MMP9	high in skin healing	anti	116
MPO	high in neutrophils	anti	117
NECTIN1	high in Chlamidial infection	pro imm	101
OLR1	NFkB activator	anti	118
PGLYRP1	high in gengivitis	anti	96
PLAU	high after thrombosis	anti	119
PRG2	eosinophils basic protein	anti	120
PTX3	increased by IL6	anti	121
RNASE2	high in inflamm, anti-viral	anti anti-imm	125
RNASE3	anti viral	anti imm	125
SPTBN1	reduces TGFb	pro	122
TM7SF3	reduces nitric oxid	pro	123
TNFAIP8	high in inflamm	anti	124

Table 2.

GENE ID	function	output on inflammation
CCL5	activates NK	pro immun
CCR4	high in asthma	pro
CCR5	activates NK	pro immun
CD28	inactivated by PD1	pro immun
CD74	increases MCHII expression	pro immun
CX3CR1	high in antifungal resp	pro immun
CXCL16	high in anti-viral resp	pro-immun
CXCR3	high in T effector	pro immun
FYN	high in inflamm/sustains NK	pro / pro imm
HAVCR2	high in anti-viral resp	pro-immun
IFNG	antiviral	pro immun
JAK3	shift from M1 to M2 resp	anti
NFATC2	increases T memory	pro immun
PDE4A	low in sepsis	anti
SERPINB9	activates CD8	pro immun
SOCS3	low in arthritis	anti
STAT5A	high in colon inflamm	pro
TLR3	anti-viral/anti-inflamm	anti / pro imm

Table 3. Table reports the comparison of several features (hematological indication, safety, cost) in different hematological drugs that might have a role in the COVID-19. Abbreviations: MPN=chronic myeloproliferative neoplasms; MAS=macrophage activation syndrome; CML=chronic myeloid leukemia; ALL=acute lymphoblastic leukemia; GIST=stromal gastro-intestinal tumor; GVHD=graft-versus-host disease; LNH=non Hodgkin's lymphoma; MM=multiple myeloma.

Table 3.

	Ruxolitinib	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ibrutinib	Begelomab	IFN
Drug formulation	os	os	os	os	os	os	IV	os
Clinical use in GVHD	XX	X	X	X	-	XX	XX	-
Use in hematological diseases	MPNs MAS	CML ALL GIST	CML ALL	CML ALL	CML	CLL MCL	GVHD	CML MPN LNH MM
Infection rate	20%	5%	11%	17%	4%	71%	10%	na
Estimated costs	++	+	+	+	+	+++	+++	+