

JAK out of the Box; The Rationale behind Janus Kinase Inhibitors in the COVID-19 setting, and their potential in obese and diabetic populations

Rahma Menshawey^a, Esraa Menshawey^a, Ayman H.K. Alserr^b and Antoine Fakhry Abdelmassih^c

The adaptive use of Janus kinase (JAK)-inhibitors has been suggested by rheumatology experts in the management of COVID-19. We recount the rationale behind their use in this setting, and the current evidence for and against their use in this review. JAK-inhibitors role in COVID-19 infection appears to be multifaceted, including preventing viral endocytosis and dampening the effect of excessive chemokines. This drug class may be able to achieve these effects at already preapproved dosages. Concerns arise regarding reactivation of latent viral infections and the feasibility of their use in those with severe disease. Most interestingly, JAK-Inhibitors may also have an additional advantage for diabetic and obese populations, where the dysregulation of JAK-signal transducer and activator of transcription pathway may

be responsible for their increased risk of poor outcomes. Targeting this pathway may provide a therapeutic advantage for these patient groups. *Cardiovasc Endocrinol Metab* 10: 80–88 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.

Cardiovascular Endocrinology & Metabolism 2021, 10:80–88

Keywords: baricitnib, COVID-19, diabetes, Janus kinase-signal transducer and activator of transcription inhibitor, obesity, ruxolitinib

^aResearch Department, Students' and Interns' Research Program (Research Accessibility Team), Cairo University Kasr al Ainy Faculty of Medicine,

^bDepartment of Vascular Surgery and ^cPediatric Cardiology Unit, Pediatrics' Department, Faculty of Medicine, Cairo University Hospital, Cairo, Egypt

Correspondence to Rahma Menshawey, MD, Research Department, Cairo University Hospitals, Cairo University, Geziret Elroda, Manial 11562, Cairo, Egypt
E-mail: rahma.a.abdelmohsen@students.kasralainy.edu.eg

Received 5 July 2020 Accepted 4 September 2020

Introduction

The urgency caused by the pandemic of coronavirus disease 2019 (COVID-19) has resulted in the frantic search and repurposing of many medications in the quest to treat it. This includes a wide array of antiparasitic, antiviral, antibiotic and immunological mediations [1–6].

COVID-19 is characterized by a state of pulmonary hyper-inflammation and cytokine storm [7], the suggested culprit of which is interleukin-6 (IL-6) as well as other cytokines [8,9]. The challenge in treating COVID-19 lies in finding the fine line where the immune system response is modulated with enough precision so that the infection is dealt with, while at the same time avoiding the detriments of an aggravated immune response. In light of this, a paradigm shift has occurred and is reshaping how we target inflammation in the setting of infection: to achieve the right response, in the right way and the right amount.

Focus on the inflammatory dysregulation, which is the driving force behind COVID-19 morbidity and mortality, has opened the grounds for drugs such as immunologicals [8].

Of particular interest are Janus kinase-signal transducer and activator of transcription (JAK-STAT) inhibitors and

their potential in treating COVID-19 patients, as initially suggested by Richardson *et al.* [10]. The JAK-STAT pathway plays a critical role in coordinating the immune response.

Furthermore, JAK-STAT pathway dysregulation is noted in obese and diabetic populations. Interestingly, among those patient groups, there exists a higher risk for more severe disease and poor outcomes in COVID-19 infection. We outline here the rationale behind the use of JAK-STAT inhibitors in the setting of COVID-19 infection, including their potential for use in diabetic and obese subgroups and provide suggestions for healthcare practitioners.

The rationale

Inflammation and viral endocytosis

The JAK-STAT pathway involves a family of proteins that are involved in a myriad of cellular processes, including cell division and immunity [11]. The importance of this pathway in defense against infection is evidenced by the fact that many organisms have adapted methods [12] that target JAK-STAT proteins for their survival. Additionally, the occurrence of some immunodeficiencies is the result of mutations in JAK interactions [13].

In the simplest terms, activation of this pathway leads to the promotion of several inflammatory products [14].

This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Upon binding of a chemokine to the JAK-receptor, a cascade of reactions is triggered [15], whereby their transcription is greatly increased (see Fig. 1). In the setting of COVID-19, the overproduction of these cytokines, especially IL-6, is responsible for the event of a cytokine storm. For this reason, immunologicals such as JAK inhibitors are being repurposed in an attempt to dampen this immune response.

JAK inhibitors have also been shown to target the specific genetic alterations observed in the COVID setting, including c-reactive protein, IL-2, IL2RB, IL6, TNF and others [16] (see Fig. 2). They also affect the endocytosis of the virus by means of blocking G-associated kinase and adaptor associated kinase 1 [17]. Artificial intelligence algorithms have pinpointed baricitinib for its affinity in this role; conveniently, it does so at already approved therapeutic dosages. Upadacitinib has been found to be the greatest at reducing levels of IL-6, via inhibition of STAT-3 [18].

The ACE2 and angiotensin II connection

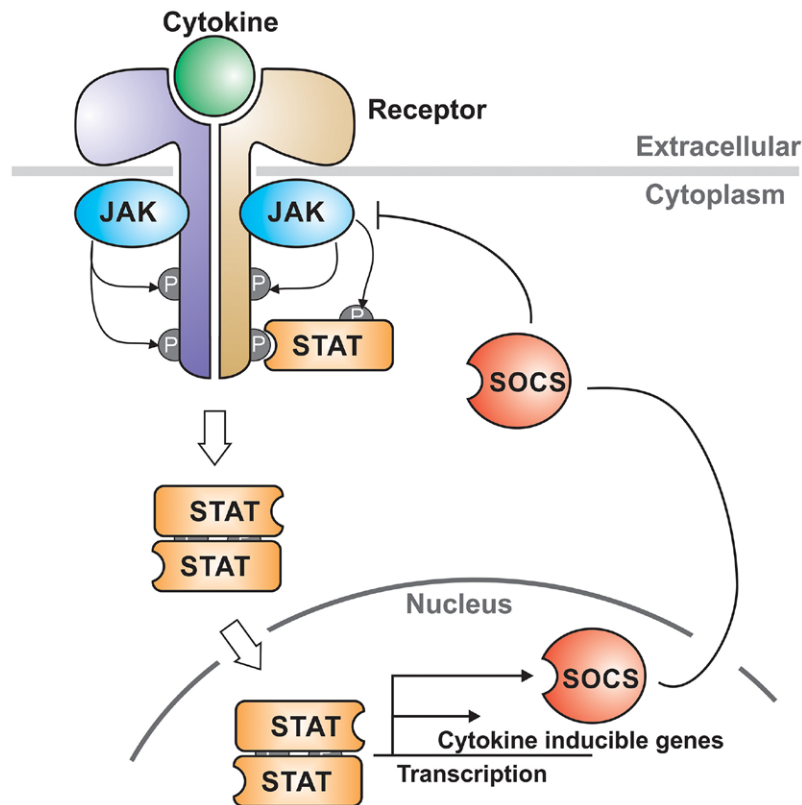
A connection exists between JAK-STATs and the trans-membrane receptor ACE2 which is the receptor

by which severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) enters body cells [19]. Upon viral entry, ACE2 becomes internalized [20]. The cytokines produced via the JAK pathway have been found to internalize ACE2 receptors, as well. Initially, it was thought that, in studies of the 2002 SARS outbreak [21], these cytokines may decrease susceptibility to infection by decreasing the availability of ACE2 receptors. However, in an already infected person, the loss of the ACE2 protective effects on vascular biology became a matter of concern. This is especially relevant in COVID, where the culprit of symptoms is owed to an inflammatory response and not due to viral load [22].

Interestingly, spike protein and ACE2 interactions activate a disintegrin metalloprotease which results in the total shedding of the ACE2 receptor from the cell surface. This results in the increase in local production and effect of angiotensin II (AII) and hyaluronan; both of which are implicated in the development of acute respiratory distress syndrome [23–26]. Production of AII itself is induced by the activation of JAK signaling [27].

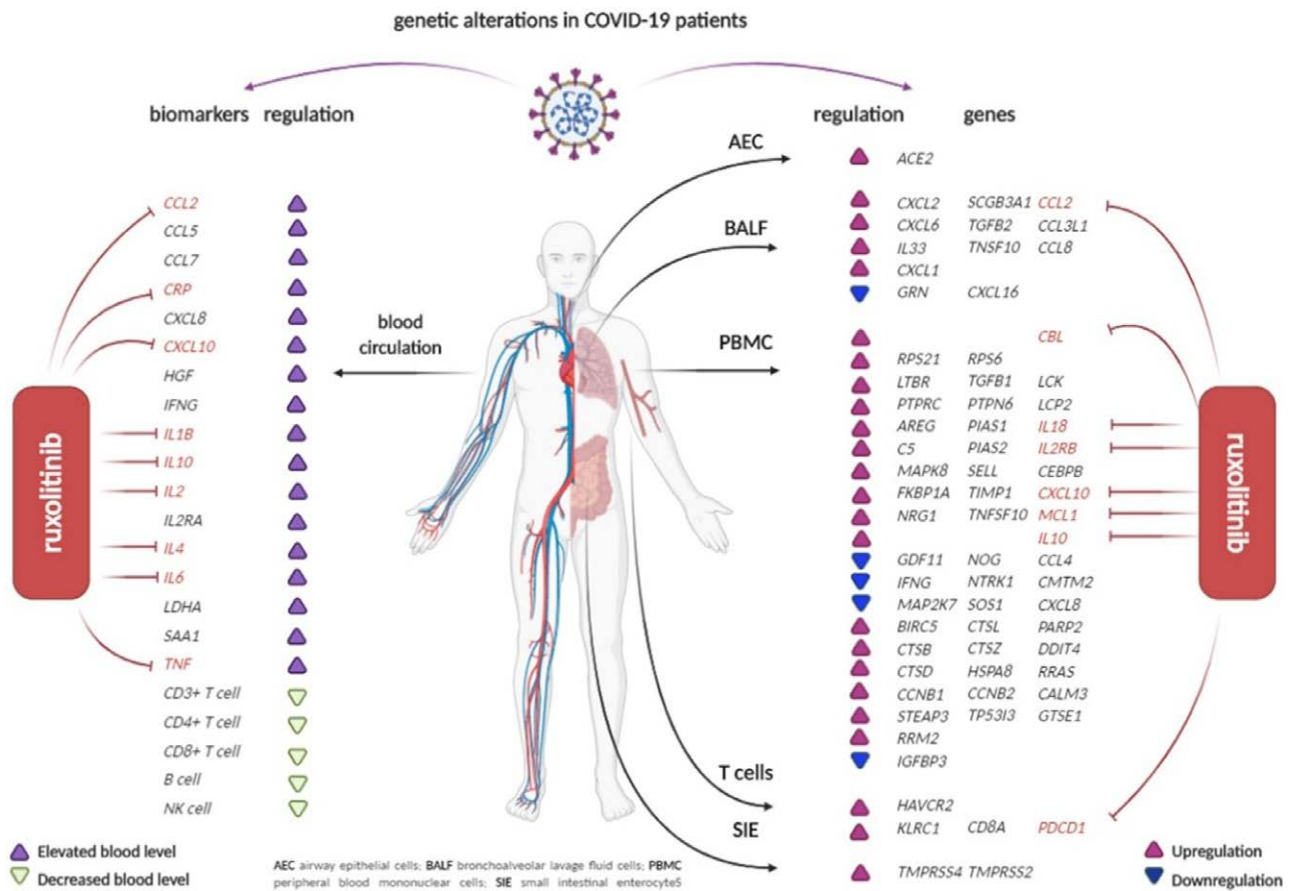
There are two polarizing hypotheses regarding the inhibition of renin angiotensin system (RAS): (1) inhibition

Fig. 1



The JAK-STAT pathway. Cytokine binds to the receptor which activates JAK-STAT. STAT homodimers are translocated into the nucleus, where they go on to upregulate the transcription of cytokine responsive genes. Reused with permission (license number: 4861540664915). JAK-STAT, Janus kinase-signal transducer and activator of transcription; SOCS, suppressor of cytokine signalling.

Fig. 2



Genetic alterations seen in COVID-19. The JAK inhibitor ruxolitinib appears to target the majority of these alterations. Image reused with permission (license number: 4861521389447). COVID-19, coronavirus disease; JAK, Janus kinase.

should prove harmful in that ACE2 receptors are increased and available for viral binding, or that (2) inhibition should prove protective by inhibiting the inflammatory/fibrotic effects of AII [28,29]. The decisive factor remains whether or not RAS blockade should increase ACE2 in humans, and in a review of the literatures, it was found that Angiotensin Receptor Blockers/Angiotensin Converting Enzyme Inhibitors did not [30–34]. These findings shift the hypothesis in favor of RAS blockade-related anti-inflammatory effects, as well as dispel fears of medication use in hypertensive patients in the setting of COVID, where they have not been associated with a higher risk of COVID-19 severity or mortality [35–38]. Additionally, the chemokines produced through the JAK pathway play a synergistic role with AII on its effects on vascular biology [39,40] (see figure 3). These effects would be irresistibly blocked with the use of JAK-STAT inhibitors.

JAK-STAT in Obese and Diabetic Populations

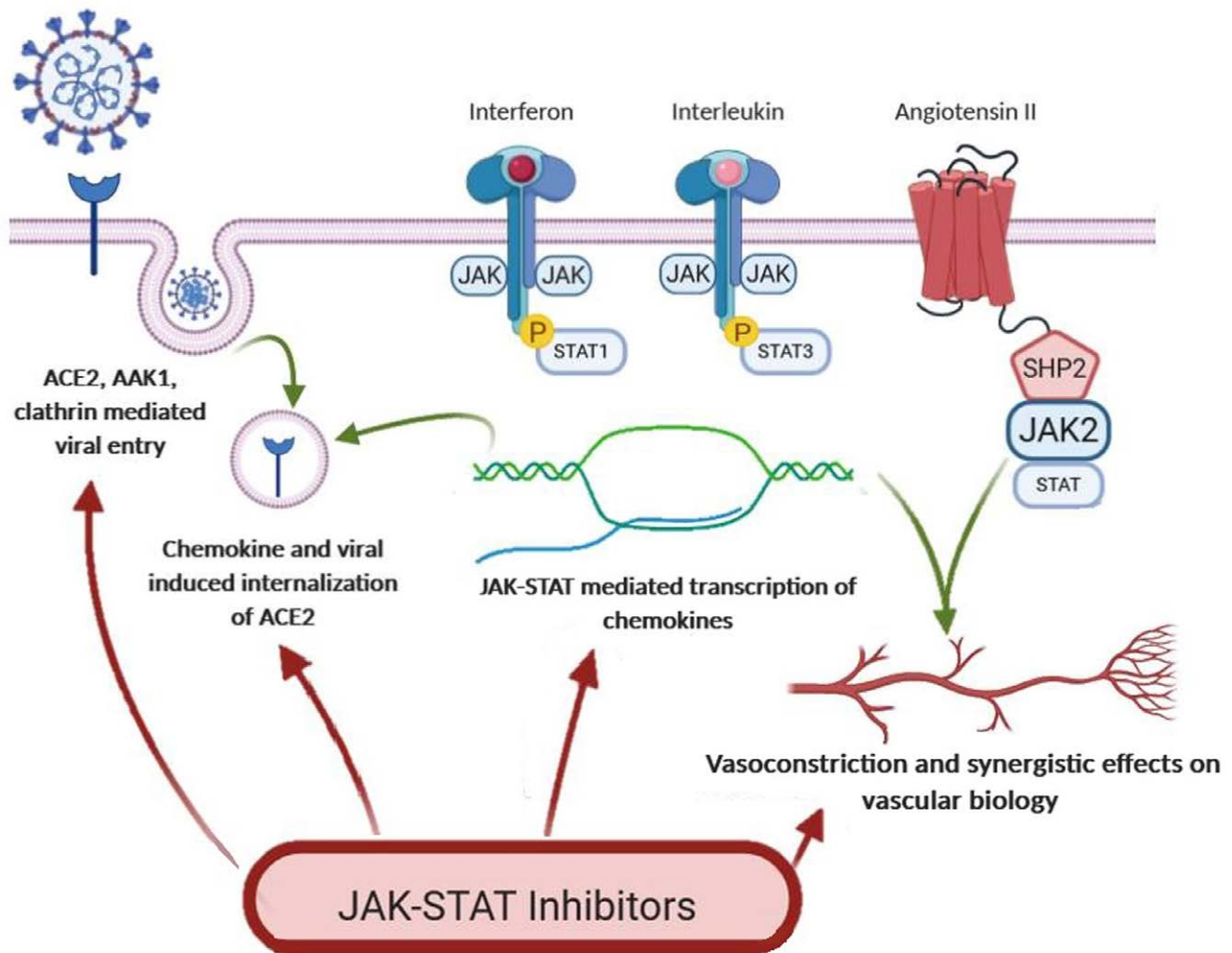
A dysregulated pathway: a common pathogenesis

The JAK-STAT signaling pathway is dysregulated in obese and diabetic patients and is implicated in disease progression.

In the brain, leptin signaling involves the JAK2 receptor and downstream signaling by STAT3. This causes increased transcription of pro-opiomelanocortin and decreased transcription of agouti related peptide and neuropeptide Y, to the effect of maintaining the anorectic response to leptin. JAK signaling also induces expression of a negative regulator of leptin expression, suppressor of cytokine signalling 3 (SOC3) [41]. In lean persons, leptin induces satiety and energy expenditure, whereas, in the obese person, there is leptin resistance despite high leptin levels, which goes on to suppress the secretion of insulin from B islet cells of the pancreas and promotes hypertension.

Mutations in JAK-STAT signaling have resulted in the development of obesity (see Fig. 4) [42]. Hepatic steatosis is, in part, regulated by JAK-STAT signaling – in particular, through its effect on the insulin-like growth factor-1 (IGF-1)/growth hormone axis [43]. STAT1 signaling has been shown to increase fatty acid uptake and steatosis. STAT5, triggered by obesity-mediated hyperinsulinemia, was shown to increase IGF-1, which exacerbates steatosis and also explains the enhanced growth rates observed in obese children and adolescents [44,45].

Fig. 3



Effect of JAK-STAT inhibition is multifaceted. It may inhibit viral endocytosis, as well as decrease the transcription of inflammatory cytokines, the presence of which is highly implicated in morbidity and mortality in COVID-19, as well as dampen the effect of these chemokines and that of angiotensin II, on vascular biology. JAK-STAT, Janus kinase-signal transducer and activator of transcription.

Knockouts in STAT pathways showed adipocyte hypertrophy and an increase in weight.

In diabetes, JAK-STAT signaling contributes to the disease process of both forms. In type 1 diabetes mellitus, immune reactions in the pancreas cause the secretion of pro-inflammatory cytokines, such as interferon- γ . IFN- γ binding to JAK induces the pathway to up-regulate the transcription of genes, including those for chemokines, BCL2 and interferon regulatory transcription factors, resulting in a pro-inflammatory environment, which affects the normal B islet cell number and function [46,47]. Additionally, STAT1 expression in B cells is required for the pathogenesis of autoimmune diabetes, as it is involved with B cell loss.

Outcomes in COVID-19: a common risk

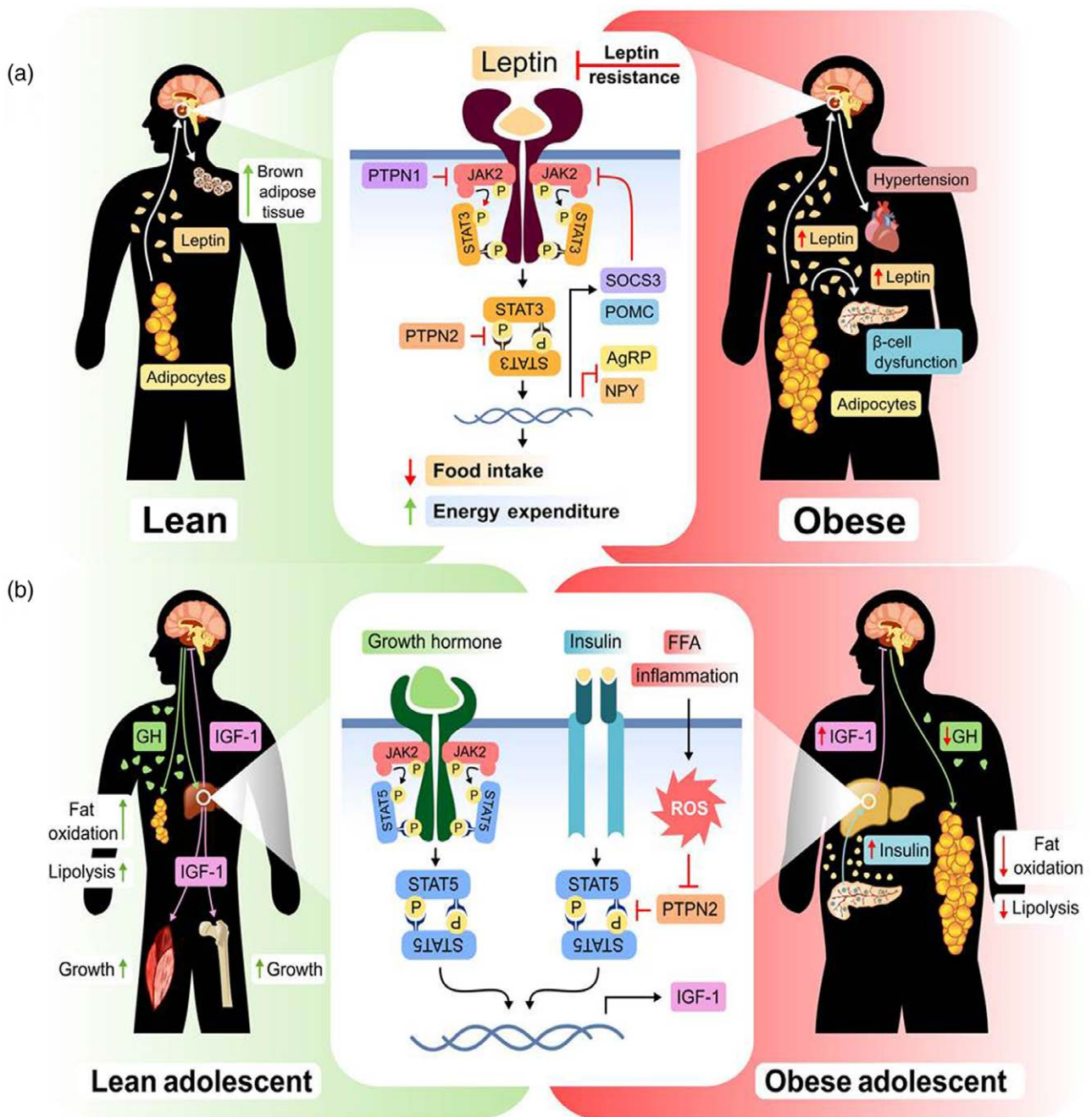
IL-6, one of the culprits involved in cytokine storm development in COVID patients, is an activator of the

JAK-STAT pathway and is increased in the serum of diabetic and obese patients. A suggestion arises where manipulation of this pathway may offer a potential therapeutic approach particularly advantageous to obese and diabetic patients.

Interestingly, these two patient groups are at higher risk of poor outcomes in the setting of COVID-19 infection. Diabetes accounted for more than 20% of ICU admissions in a cohort study in China [48]. In Italy, two-thirds of those who died with SARS-Cov-2 had diabetes [49]. Obesity has been associated with a three-fold increased risk of severe COVID infection [50]. Visceral and liver fat is independently correlated with increased levels of IL-6, the key pro-inflammatory cytokine involved in the inflammatory storm [50,51].

Both diabetes and obesity potentiate cardiovascular risk factors, which are recognized to increase the risk of poor outcomes in the setting of COVID-19. In both patient

Fig. 4



JAK-STAT signaling pathway in obesity. (a) Leptin binds to its receptor and induces JAK-STAT signaling pathway. In the lean person, leptin causes satiety and energy expenditure. In the obese person, there is leptin resistance in spite of high levels of leptin. This hyperleptinemia is further implicated in the inhibition of insulin release from the B islet cells in the pancreas. Aberrant JAK-STAT signaling is implicated in the development of obesity. (b) JAK-STAT signaling is also involved in the growth hormone/insulin-like growth factor-1 axis. Free fatty acid and inflammatory signaling are also implicated in the activation of JAK pathway. All of which is the end result of increased adipose tissue accumulation. Image reused with permission (license number: 4862101271475). JAK-STAT, Janus kinase-signal transducer and activator of transcription.

groups, there is limited ‘ability to evoke an appropriate metabolic response upon immunologic challenge’ [52]. Given the dysregulated JAK-STAT pathway in these patient groups, it may be another potential mechanism that explains why these groups have increased risk of poor outcomes in infection.

JAK-STAT Inhibitors; Are They Feasible? Use in the obese and diabetic

As mentioned before, the several JAK-STAT pathways implicated in the development of both obesity and diabetes have garnered the suggestion that inhibition of this pathway may provide an advantage for their use in these

patient groups. Brosius *et al.* have outlined the potential of JAK inhibition in diabetic patients. JAK inhibition serves both an anti-inflammatory purpose as well as aid in renin angiotensin aldosterone system inhibition, uniquely treating diabetic kidney disease (DKD). Safety concerns arise when considering long-term therapy, especially with the potential of aggravating anemia, which often complicates those with DKD. Additionally, activation of some STAT pathway in diabetic patients can occur independent of JAK activation; intervention more distally in this cascade may be required [53].

In obesity, JAK inhibition has been shown to induce the browning of white adipose tissue as well as amelioration of obesity-related metabolic disorders *in vitro*. In murine models, thermogenic capacity was increased, whereas chronic inflammation of adipose was not ameliorated. JAK inhibition showed preserved insulin sensitivity, as well as a significant reduction in free fatty acids and serum triglycerides [54]. Interestingly, obesity appears to influence the effectiveness of therapies that target the immune response. JAK inhibitor use has shown a negative impact on low disease activity in obese patients with rheumatoid arthritis. Similarly, obese patients were found to have an inferior response to anti-TNF therapy in rheumatoid arthritis (RA), suggesting the role of obesity as an effect modifier and the need for weight loss in those with underlying immune-mediated inflammatory diseases who become resistant to immunological therapy [55].

Use in the setting of COVID-19

JAK-STAT inhibitors in the treatment of COVID-19 patients offer a potential advantage in that they achieve their effects at already approved dosages, and some have minimal protein binding allowing for combination therapy with antiretrovirals [56]. However, evidence suggests that JAK-STAT inhibitors may cause reflare of latent viral infections, such as herpes zoster. Other concerns include lipid profile derangement, as well as decreases in neutrophils, lymphocytes, NK cells, platelets, and increases in transaminases and serum creatinine levels, all of which are mild and reversible [57]. However, their safety profile is still comparable and acceptable with other biologic drugs [58,59].

In the setting of COVID-19, Randomized Controlled Trials (RCTs) are many and still ongoing (i.e. tofacitinib [60], NCT04332042; baricitinib [61], NCT04321993, NCT04345289, NCT04320277, NCT04346147, NCT04340232; ruxolitinib, NCT04348695, NCT04331665, NCT04337359, NCT04338958, NCT04334044, NCT04348071).

Cantini *et al.* [62] assessed the safety profile of baricitinib combined with lopinavir–ritonavir in moderate COVID-19 pneumonia. Patients were treated for 2 weeks with baricitinib 4 mg/day added to lopinavir–ritonavir therapy. Treatment was well tolerated with no serious adverse

events. Clinical characteristics and respiratory functions were much improved at weeks 1 and 2 compared to baseline. There were less ICU transfers, more discharges and more negative swabs on discharge in those treated with JAK inhibitors. No infections, cardiovascular or hematological adverse events occurred after 2 weeks of treatment.

Concerns about side effects

Perhaps the most alarming concern regarding the use of JAK-inhibitors is due to their effect of inhibiting cytokines that are essential in the response against pathogens, especially interferons. There is still some argument regarding the use of immune modulators in the setting of COVID-19 acute infection. For example, some studies involving corticosteroids have yet to find any difference in clinical outcomes, whereas some report findings of negative outcomes [63]. Without the essential action of interferons on infection, patients may be put at unnecessary risk of bacterial superinfection, and prolonged and more severe disease course. Therefore, all medications that intend to target the various inflammatory immune pathways in the setting of infection need to be approached with considerable caution.

Reactivation of latent infection

Attention has been called to concerns of reactivations of latent viral infection in light of new COVID-19 patient data, where neutrophil and lymphocyte counts were found to be close to the threshold value in patients admitted to ICU and non-survivors [48,64–66].

Harigai *et al.* [67,68] have studied reactivations of infections in RA patients on baricitinib; monitoring for hepatitis B virus DNA in those with latent infection is recommended. The risk of tuberculosis (TB) was strongly associated with whether or not patients belonged to endemic TB areas. Screening is recommended in those with latent TB. The general risks involved with JAK-STAT inhibitors include an increased risk for herpes zoster common to all JAK inhibitors [68]. Fundamentally, there is no difference between JAK inhibitors and other disease-modifying anti-rheumatic drugs with regard to infections; except for herpes zoster [69], with the risk being highest with baricitinib.

Concerns for coagulopathy and cardiovascular incident

Given the setting of increased coagulopathy in COVID-19 patients, the Food and Drug Administration (FDA) has warned about an increased risk for thromboembolism with the use of JAK-STAT inhibitors [70]. The finding of the increased risk of pulmonary embolism and death in RA patients was seen with the use of tofacitinib 10 mg twice daily dose. Table 1 highlights information on the only three JAK inhibitors with FDA approval, along with recommendations [60,61,71,72].

Table 1 Drug data on suggested approved JAK-inhibitors^a with Food and Drug Administration approval

Drug	Dosages	Target	Safety	Recommendations
Tofacitinib	5 mg twice daily for rheumatoid arthritis (11 mg extended release available) 10 mg for UC	JAK1 JAK3	Risk of PE and death in rheumatoid arthritis patients on 10 mg. CYP3A4 substrate with CYP inhibition potential. No association with QT prolongation. Potential risk of gastrointestinal perforation in patients with intestinal diverticulum/diverticulitis.	Frequent monitoring for coagulopathy, and symptom of PE. If serum aminotransferase elevated more than 5x upper limit, cease medication or dose reduction. Dose adjustment necessary in case of hepatic impairment. Dose adjustment warranted if co-administered with CYP3A4 inhibitors, namely fluconazole and ketoconazole.
Baricitinib	2 mg twice daily for rheumatoid arthritis.	JAK1 JAK 2	Excreted mostly unchanged in urine. Not affected by CYP inhibitors or inducers. Limited incidence of decreased hemoglobin, increased LDL, HDL, creatinine, creatine phosphokinase. Renal secretion affected by probenecid. No association with QT prolongation. Potential risk of gastrointestinal perforation in patients with intestinal diverticulum/diverticulitis.	If serum aminotransferase elevated more than 5x upper limit, cease medication or dose reduction. No cross reactivity in risk for hepatic injury between other DMARDs or other JAKinibs; may consider combination therapy. Low potential for drug–drug interactions. Dose reduction to 2 mg for patients on OAT3 inhibitors Dose reduction if renal clearance 30–60 mL/min. Not recommend if creatinine clearance <30 mL/min. Interrupt dose if ALC less than 500. or ANC less than 100 or Hb less than 8. Monitor for increase in lipid parameters. No dose adjustment needed for renal or hepatic patients.
Upadacitinib	15 mg	JAK1	CYP3A4 substrate. At clinical concentrations, no known inhibition of drug metabolizing enzymes or transporters. Mild-moderate hepatic impairment, and renal impairment have no effects on pharmacodynamics. No QT prolongation.	Interrupt dose if ALC less than 500 or ANC less than 100 or Hb less than 8.

^aALC, absolute lymphocyte count; ANC, absolute neutrophil count; DMARDs, disease modifying anti-rheumatic drugs. ALL JAK inhibitors are contraindicated during pregnancy. Women of child bearing age should, should initiate contraceptives at least 1 week before use. Avoid their use in patients who are breastfeeding.

Scott *et al.* [73] outlined the risk of thromboembolic events with JAK inhibitor use. The thromboembolic risk was found to be 5 per 1000 patient-years with the use of baricitinib 4 mg daily. In another study, no association was found between baricitinib use and major adverse cardiovascular event, arterial thrombotic event and congestive heart failure [74].

Tolerability

Studies on tolerability to JAK-inhibitors revealed that the most frequent treatment requiring adverse events were nausea, headache and dyspepsia. Nausea was most common in those treated with tofacitinib compared to placebo, and in all patients, it was only mild, occurred in the first hour of dosing, and resolved on day 1. There were no deaths, severe or serious adverse events, or discontinuations. Additionally, there were no events of neutropenia, leucopenia, infection or anemia. No subjects had liver enzyme levels >3 times upper limit, or creatinine clearance >1.3 times upper limit of normal. No clinically relevant changes were seen in white blood cell count or any other lab investigations. No significant changes were found regarding heart rate, respiratory rate, blood pressure and no significant ECG findings [75]. Trials involving baricitinib showed the most common adverse effects were URTI, headache, blood creatinine kinase increase, diarrhea, nausea, and bronchitis. Temporary interruptions of JAK inhibitor therapy in RA patients, with later re-initiation of therapy, were associated with an increase in disease symptoms [76].

Conclusion

JAK-STAT plays a critical role in modulating the immune system [6] by providing necessary and vital chemokines that help fend off infection. However, given the setting of COVID-19, which is highlighted by a state of over inflammation, JAK-STAT pathway activation comes at a steep price; an aggravated immune response likely to the detriment of the patient. The polarizing decision to either dampen or enhance the immune response is still a matter of argument; however, given the overwhelming evidence that an erratic immune response is the likely culprit of increased morbidity and mortality in COVID-19 patients, the playing field has opened up for a vast variety of medications, which target the pathways of inflammation. It would appear that inhibiting the JAK-STAT pathway has some potential [23]. Its multifaceted effects, from lowering IL6, to inhibiting viral endocytosis, and dampening the effects of AGII, as well as a specific potential benefit for obese and diabetic patient groups, suggests that JAK-STAT inhibitors are definitely worthy of consideration. Concerns arise due to their side effects, which most notably include inhibiting interferon production. So far, baseline use of these medications has not been shown to increase the risk of poor outcomes in COVID-19.

Clinicians considering the use JAK-STAT inhibitors should do so with care and caution, with frequent monitoring for flares of latent infection and potential lab derangements. It is not recommended that JAK-STAT inhibitors be used in asymptomatic patients, as 80% of

these patients are generally capable of clearing infection via endogenous antiviral mechanisms [17]. Furthermore, in patients whose disease progression is more than moderate, that is requiring ICU admission, dose reduction or avoidance completely is recommended given the fears of co-infection/reactivation of latent infection, as well as concerns for lymphocytopenia that may be associated with this disease stage.

Long-term studies are needed to further establish and cement the use of JAK-STAT inhibitors in the fight against COVID-19. The results of ongoing RCT involving JAK-STAT inhibitor use in COVID-19 patients will enrich and enhance our understanding of this drug class.

An exaggerated or an inhibited JAK-STAT response has been suggested in the great majority of immune-related pathologies. Finding a delicate balance will prove to be decisive.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

- Touret F, de Lamballerie X. Of chloroquine and COVID-19. *Antiviral Res* 2020; **177**:104762.
- Jean SS, Lee PI, Hsueh PR. Treatment options for COVID-19: the reality and challenges. *J Microbiol Immunol Infect* 2020; **53**:436–443.
- Wang X, Cao R, Zhang H, Liu J, Xu M, Hu H, *et al.* The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 *in vitro*. *Cell Discov* 2020; **6**:28.
- Cao B, Wang Y, Wen D, Liu W, Wang J, Fan, *et al.* A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020; **382**:1787–1799.
- Ford N, Vitoria M, Rangaraj A, Norris SL, Calmy A, Doherty M. Systematic review of the efficacy and safety of antiretroviral drugs against SARS, MERS, or COVID-19: initial assessment. *J Int AIDS Soc* 2020; **23**:e25489.
- Russell B, Moss C, George G, Santaolalla A, Cope A, Papa S, *et al.* Associations between immune-suppressive and stimulating drugs and novel COVID-19 – a systematic review of current evidence. *Ecancer* 2020; **14**:1022.
- Panigrahy D, Gilligan MM, Huang S, Gartung A, Cortés-Puch I, Sime PJ, *et al.* Inflammation resolution : a dual-pronged approach to averting cytokine storms in COVID-19 ? *Cancer Metastasis Rev* 2020; **39**:337–340.
- Zhang C, Wu Z, Jia-Wen L, Zhao H, Wang G-Q. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonist tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents* 2020; **55**:105954.
- Michot J, Albiges L, Chaput N, Saada V, Pommeret F, Griscelli F, *et al.* Tocilizumab, an anti-IL6 receptor antibody, to treat Covid-19-related respiratory failure: a case report. *Ann Oncol* 2020; **31**:961–964.
- Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, Richardson P. Comment COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis* 2020; **20**:400–402.
- Seif F, Khoshmirisafa M, Aazami H, Mohsenzadegan M, Sedighi G, Bahar M. The role of JAK-STAT signaling pathway and its regulators in the fate of T helper cells. *Cell Commun Signal* 2017; **15**:23.
- Fleming SB. Viral inhibition of the IFN-induced JAK/STAT signalling pathway: development of live attenuated vaccines by mutation of viral-encoded IFN antagonists. *Vaccines* 2016; **4**:23.
- Berg LJ. The “bubble boy” paradox: an answer that led to a question. *J Immunol* 2008; **181**:5815–5816.
- Ivanov P, Emará MM, Villen J, Gygi SP, Anderson P. Angiogenin-induced tRNA fragments inhibit translation initiation. *Mol Cell* 2012; **43**:613–623.
- Aaronson DS, Horvath CM. A road map for those who don't know JAK-STAT. *Science* 2002; **296**:1653–1655.
- Bagca GB, Avci CB. The potential of JAK/STAT pathway inhibition by ruxolitinib in the treatment of COVID-19. *Cytokine Growth Factor Rev* 2020; **54**:51–62.
- Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, *et al.* Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet* 2020; **395**:e30–e31.
- Napolitano M, Fabbrocini G, Patruño C. Reply: potential role of Janus kinase inhibitors in COVID-19. *J Am Acad Dermatol* 2020; **83**:e65.
- Jia HP, Look DC, Shi L, Hickey M, Pewe L, Netland J, *et al.* ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. *J Virol* 2005; **79**:14614–14621.
- Lang AD, Osterhaus ADME, Haagmans BL. Interferon- γ and interleukin-4 downregulate expression of the SARS coronavirus receptor ACE2 in Vero E6 cells. *Virology* 2006; **353**:474–481.
- Imai Y, Kuba K, Penninger JM. Review angiotensin-converting enzyme 2 in acute respiratory distress syndrome. *Cell Mol Life Sci* 2012; **64**:2006–2012.
- AbdelMassih AF, Ramzy D, Nathan L, Aziz S, Ashraf M, Youssef NH, *et al.* Possible molecular and paracrine involvement underlying the pathogenesis of COVID-19 cardiovascular complications. *Cardiovasc Endocrinol Metab* 2020; **9**:121–124.
- Seif F, Aazami H, Khoshmirisafa M, Kamali M, Mohsenzadegan M, Pornour M, Mansouri D. JAK Inhibition as a new treatment strategy for patients with COVID-19. *Int Arch Allergy Immunol* 2020; **181**:467–475.
- Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, *et al.* A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus – induced lung injury. *Nat Med* 2005; **11**:875–879.
- Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, *et al.* Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005; **436**:112–116.
- Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med* 2020; **46**:586–590.
- Sayeski PP, Ali MS, Safavi A, Lyles M, Kim SO, Frank SJ, Bernstein KE. A catalytically active Jak2 is required for the angiotensin II-dependent activation of Fyn. *J Biol Chem* 1999; **274**:33131–33142.
- South AM, Tomlinson L, Edmonston D, Hiremath S, Sparks MA. Controversies of renin-angiotensin system inhibition during the COVID-19 pandemic. *Nat Rev Nephrol* 2020; **19**:6–8.
- Busse LW, Chow JH, Mccurdy MT, Khanna AK, Coronavirus K, li A. COVID-19 and the RAAS – a potential role for angiotensin II ? *Crit Care* 2020; **24**:136.
- Sriram K, Insel PA. Risks of ACE inhibitor and ARB usage in COVID-19: evaluating the evidence. *Clin Pharmacol Ther* 2020; **108**:236–214.
- Mizuri S, Ohashi Y. ACE and ACE2 in kidney disease. *World J Nephrol* 2015; **4**:74–82.
- Mariana PC, Ramona PA, Ioana BC, Diana M, Claudia C, Stefan VD, Maria KI. Urinary angiotensin converting enzyme 2 is strongly related to urinary nephrin in type 2 diabetes patients. *Int Urol Nephrol* 2016; **48**:1491–1497.
- Epelman S, Tang WH, Chen SY, Van Lente F, Francis GS, Sen S. Detection of soluble angiotensin-converting enzyme 2 in heart failure: insights into the endogenous counter-regulatory pathway of the renin-angiotensin-aldosterone system. *J Am Coll Cardiol* 2010; **52**:750–754.
- Úri K, Fagyas M, Kertész A, Borbély A, Jenei C, Bene O, *et al.* Circulating ACE2 activity correlates with cardiovascular disease development. *J Renin Angiotensin Aldosterone Syst* 2016; **17**:1470.
- Mehta N, Kalra A, Nowacki AS, Anjewierden S, Han Z, Bhat P, *et al.* Association of use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; **2019**:1–7.
- Zhang X, Yu J, Pan L, Jiang H. ACEI/ARB use and risk of infection or severity or mortality of COVID-19: a systematic review and meta-analysis. *Pharmacol Res* 2020; **158**:104927.
- Meng J, Xiao G, Zhang J, He X, Ou M, Bi J, *et al.* Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. *Emerg Microbes Infect* 2020; **9**:757–760.
- Tadic M, Cuspidi C, Mancina G, Oro D, Grassi G. COVID-19, hypertension and cardiovascular diseases: should we change the therapy? *Pharmacol Res* 2020; **158**:104906.
- Lee DL, Sturgis LC, Labazi H, Osborne JB Jr, Fleming C, Pollock JS, *et al.* Angiotensin II hypertension is attenuated in interleukin-6 knockout mice. *Am J Physiol Heart Circ Physiol* 2006; **290**:H935–H941.
- Satou R, Gonzalez-Villalobos RA. JAK-STAT and the renin-angiotensin system: the role of the JAK-STAT pathway in blood pressure and intrarenal renin-angiotensin system regulation. *JAKSTAT* 2012; **1**:250–256.

- 41 Lee JY, Muenzberg H, Gavrilova O, Reed JA, Berryman D, Villanueva EC, et al. Loss of cytokine-STAT5 signaling in the CNS and pituitary gland alters energy balance and leads to obesity. *PLoS One* 2008; **3**:e1639.
- 42 Rasmussen MH. Obesity, growth hormone and weight loss. *Mol Cell Endocrinol* 2010; **316**:147–153.
- 43 Ren D, Li M, Duan C, Rui L. Identification of SH2-B as a key regulator of leptin sensitivity, energy balance, and body weight in mice. *Cell Metab* 2005; **2**:95–104.
- 44 Martínez de Icaya P, Fernández C, Vázquez C, del Olmo D, Alcázar V, Hernández M. IGF-1 and its binding proteins IGFBP-1 and 3 as nutritional markers in prepubertal children. *Ann Nutr Metab* 2000; **44**:139–143.
- 45 Moran A, Jacobs DR Jr, Steinberger J, Cohen P, Hong CP, Prineas R, Sinaiko AR. Association between the insulin resistance of puberty and the insulin-like growth factor-1/growth hormone axis. *J Clin Endocrinol Metab* 2002; **87**:4817–4820.
- 46 Gurzov EN, Stanley WJ, Pappas EG, Thomas HE, Gough DJ. The JAK/STAT pathway in obesity and diabetes. *FEBS J* 2016; **283**:3002–3015.
- 47 Eizirik DL, Colli ML, Ortis F. The role of inflammation in insulinitis and beta-cell loss in type 1 diabetes. *Nat Rev Endocrinol* 2009; **5**:219–226.
- 48 Zhou F, Yu T, Du R, Fan G, Liu Z, Xiang J, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **6736**:1–9.
- 49 Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? *Lancet* 2020; **395**:1225–1228.
- 50 Gao F, Zheng KI, Wang X, Sun Q-F, Pan K-H, Wang T-Y, et al. Obesity is a risk factor for greater COVID-19 severity. *Diabetes Care* 2020; **43**:e72–e74.
- 51 van der Poorten D, Milner KL, Hui J, Hodge A, Trenell MI, Kench JG, et al. Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. *Hepatology* 2008; **48**:449–457.
- 52 Naveed S, McInnes IB, McMurray JJV. Obesity a risk factor for severe COVID-19 infection: multiple potential mechanisms. *Circulation* 2020; **142**:4–6.
- 53 Brosius FC, Tuttle KR, Kretzler M. JAK inhibition in the treatment of diabetic kidney disease. *Diabetologia* 2016; **59**:1624–1627.
- 54 Qurania KR, Ikeda K, Wardhana DA, Barinda AJ, Nugroho DB, Kuribayashi Y, et al. Systemic inhibition of Janus kinase induces browning of white adipose tissue and ameliorates obesity-related metabolic disorders. *Biochem Biophys Res Commun* 2018; **502**:123–128.
- 55 Singh S, Facciorusso A, Singh AG, Vande Castele N, Zarrinpar A, Prokop LJ, et al. Obesity and response to anti-tumor necrosis factor- α agents in patients with select immune-mediated inflammatory diseases: a systematic review and meta-analysis. *PLoS One* 2018; **13**:e0195123.
- 56 Favalli EG, Biggoggero M, Maioli G, Caporali R. Baricitinib for COVID-19: a suitable treatment? *Lancet Infect Dis* 2020; **3099**:30262.
- 57 Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. *Nat Rev Rheumatol* 2017; **13**:320.
- 58 Fragoulis GE, McInnes IB, Siebert S. JAK-inhibitors. New players in the field of immune-mediated diseases, beyond rheumatoid arthritis. *Rheumatology* 2019; **58**:i43–i54.
- 59 Choy EH. Clinical significance of Janus kinase inhibitor selectivity. *Rheumatology* 2019; **58**:953–962.
- 60 Vyas D, Dell KMO, Bandy JL, Boyce EG. Tofacitinib: the first Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis. *Ann Pharmacother* 2013; **47**:1524–1531.
- 61 Mayence A, Eynde JJV. A baricitinib: a 2018 novel FDA-approved molecule inhibiting Janus kinases. *Pharmaceuticals* 2019; **12**:37.
- 62 Cantini F, Niccoli L, Matarrese D, Nicasri E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: a pilot study on safety and clinical impact. *J Infect* 2020; **81**:318–356.
- 63 Veronese N, Demurtas J, Yang L, Tonelli R, Barbagallo M, Lopalco P, et al. Use of corticosteroids in coronavirus disease 2019 pneumonia: a systematic review of the literature. *Front Med* 2020; **7**:170.
- 64 Praveen D, Puvvada RC, Aanandhi V M. Janus kinase inhibitor baricitinib is not an ideal option for management of COVID-19. *Int J Antimicrob Agents* 2020; **55**:105967.
- 65 Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus – infected pneumonia in Wuhan, China. *JAMA* 2020; **323**:1061–1069.
- 66 Huang C, Wang Y, Li X, Ren K, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**:497–506.
- 67 Harigai M, Winthrop K, Takeuchi T, Hsieh T-Y, Chen Y-M, Smolen JS, et al. Evaluation of hepatitis B virus in clinical trials of baricitinib in rheumatoid arthritis. *RMD Open* 2020; **6**:e001095.
- 68 Harigai M. Growing evidence of the safety of JAK inhibitors in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2019; **58**:i34–i42.
- 69 Bechman K, Subesinghe S, Norton S, Atzeni F, Galli M, Cope AP, et al. A systematic review and meta-analysis of infection risk with small molecule JAK inhibitors in rheumatoid arthritis. *Rheumatology (Oxford)* 2019; **58**:1755–1766.
- 70 Jamilloux Y, Henry T, Belot A, Viel S, Fauter M, El Jammal T, et al. Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. *Autoimmun Rev* 2020; **19**:102567.
- 71 Biggoggero M, Becciolini A, Crotti C, Agape E, Favalli EG. Upadacitinib and filgotinib: the role of JAK1 selective inhibition in the treatment of rheumatoid arthritis. *Drugs Context* 2019; **8**:1–12.
- 72 Veeravalli V, Dash RP, Thomas JA, Babu RJ, Madgula LMV, Srinivas NR. Critical assessment of pharmacokinetic drug-drug interaction potential of tofacitinib, baricitinib and upadacitinib, the three approved Janus kinase inhibitors for rheumatoid arthritis treatment. *Drug Saf* 2020; **43**:711–725.
- 73 Scott IC, Hider SL, Scott DL. Thromboembolism with Janus kinase (JAK) inhibitors for rheumatoid arthritis: how real is the risk? *Drug Saf* 2018; **41**:645–653.
- 74 Taylor PC, Weinblatt ME, Burmester GR, Rooney TP, Witt S, Walls CD, et al. Cardiovascular safety during treatment with baricitinib in rheumatoid arthritis. *Arthritis Rheumatol* 2019; **71**:1042–1055.
- 75 Krishnaswami S, Boy M, Chow V, Chan G. Safety, tolerability, and pharmacokinetics of single oral doses of tofacitinib, a Janus kinase inhibitor, in healthy volunteers. *Clin Pharmacol Drug Dev* 2015; **4**:83–88.
- 76 Emery P, Tanaka Y, Cardillo T, Schlichting D, Rooney T, Beattie S, et al. Correction to: temporary interruption of baricitinib: characterization of interruptions and effect on clinical outcomes in patients with rheumatoid arthritis. *Arthritis Res Ther* 2020; **22**:166.