Cancer vs. SARS-CoV-2 induced inflammation, overlapping functions, and pharmacological targeting

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Abstract

Inflammation is an intrinsic defence mechanism triggered by the immune system against infection or injury. Chronic inflammation allows the host to recover or adapt through cellular and humoral responses, whereas acute inflammation leads to cytokine storms resulting in tissue damage. In this review, we present the overlapping outcomes of cancer inflammation with virus-induced inflammation. The study emphasises how anti-inflammatory drugs that work against cancer inflammation may work against the inflammation caused by the viral infection. It is established that the cytokine storm induced in response to SARS-CoV-2 infection contributes to disease-associated mortality. While cancer remains the second among the diseases associated with mortality worldwide, cancer patients’ mortality rates are often observed upon extended periods after illness, usually ranging from months to years. However, the mortality rates associated with COVID-19 disease are robust. The cytokine storm induced by SARS-CoV-2 infection appeared to be responsible for the multi-organ failure and increased mortality rates. Since both cancer and COVID-19 disease share overlapping inflammatory mechanisms, repurposing some anticancer and anti-inflammatory drugs for COVID-19 may lower mortality rates. Here, we review some of these inflammatory mechanisms and propose some potential chemotherapeutic agents to intervene in them. We also discuss the repercussions of anti-inflammatory drugs such as glucocorticoids and hydroxychloroquine with zinc or antiviral drugs such as ivermectin and remdesivir against SARS-CoV-2 induced cytokine storm. In this review, we emphasise on various possibilities to reduce SARS-CoV-2 induced cytokine storm.

Keywords Cancer · SARS-CoV-2 · COVID-19 · Inflammation · Cytokines

Immune system

The word “immune” indicates resistance developed by the host system to toxic compounds, foreign particles, and infections from the microorganisms (Parkin and Cohen 2001; Medzhitov 2007; Chaplin 2010). In gross terms, immunity refers to a host defence mechanism, which is thought to have advanced with the evolution. While unicellular organisms are equipped with specific enzymes and inhibitors to distinguish and eliminate non-self from self, the multi-cellular organisms involve cells, tissues, and blood for this purpose. Due to increased cellular complexity, vertebrates exhibit coordinated cellular defence functions involving different immune cells (Danilova 2006; Boehm and Swann 2014).

Cancer immunity

Cancer is a disease of uncontrolled cell proliferation, which primarily emerges from acquired genetic mutations and epigenetic alterations in oncogenes and tumour suppressors upon exposure to viral counterparts, UV irradiation, and carcinogens (Butel 2000; Baglia and Munger 2018; Pfeifer 2020). The cells harboring these mutations get adapted while bypassing the host immune response (Costello et al. 1999; Seliger 2005). Like cell cycle checkpoints that are deregulated in cancers to facilitate uncontrolled cell proliferation. The lymphocytes go through clonal selection and expansion to produce a subgroup of immunoglobulins to act against foreign bodies or antigens (Cooper and Alder 2006; Schroeder and Cavacini 2010). The T-cells regulate innate immune response while B-cells regulate adaptive immune response (Kaufmann 2019).
(Hanahan and Weinberg 2011), the altered immune checkpoints take care of anticancer immunity (Vinay and Kwon 2018). It could be the reason, in addition to targeting the signal transduction pathways that are identified as signatures of cancer (Bild et al. 2006), the monoclonal antibodies (MABs) and their conjugates against mutated gene products appear to act against tumours (Adams and Weiner 2005). The anticancer immune response is also associated with induced inflammatory response and benefits cancer survival and spread (Balkwill 2006; Mantovani et al. 2008). The chronic inflammation caused by cancer cells can trigger neoplastic transformation in the bystander cells (Coussens and Werb 2002; Greten and Grivennikov 2019). The elevated inflammatory responses are associated with increased cytokine levels, contributing to cancer progression (Chen and Mellman 2013; D’Elia et al. 2013). Therefore, interfering with the cytokine response is considered an alternate or adjuvant anticancer treatment strategy (Yao et al. 2014; Nakamura and Smyth 2017).

Cancer by viral infections

Many viral infections in the host are propagated by hijacking the host defence machinery. Viral infections can induce mutations in the regulatory proteins such as oncogenes and tumour suppressors. It is established that many RNA (Butel 2000) or DNA (Fey and Larsen 1988) virus infections, such as human papilloma (HPV) (Araldi et al. 2018), human immunodeficiency syndrome virus (HIV) (Yarchoan and Uldrick 2018), Kaposi’s sarcoma-associated herpesvirus (KSHV) (Gonçalves et al. 2017), hepatitis C virus (HCV) (Benkheil et al. 2018), human polyomavirus (JCV) (Delbue et al. 2017), and hepatitis B virus (HBV) (Levrero and Zucman-Rossi 2016) infections, can cause cancers (Fig. 1). The most common viral infection by HPV is shown to cause age-related cancer progression in women indicating that the compromised immune system is permissive to virus spread (Castellsagué 2008). Consequently, old age has been identified as a risk factor for cancer (White et al. 2014a). The Adenovirus (McAllister et al. 1972) and SV40 polyomavirus (Poulin and DeCaprio 2006) are also shown to cause cancers.

Mechanisms of virus-induced cancer

Both RNA and DNA viruses can cause cancer in the host. The viral genes can permanently incorporate into the host genome and facilitate deregulated cellular mechanisms favouring tumour growth (Vogt et al. 1997; Temin and Mizutani 1970). Among the two classes of viruses, the transforming virus will have a proto-oncogenic counterpart, and upon mutation, it can transduce into host cells to induce cellular transformation, whereas non-transforming virus can introduce a strong viral promoter or viral gene into the host cell to trigger the transcription of growth promoting factors (Fan 2011; Vogt 2012). The RNA and DNA viruses are dependent on host transcriptional machinery for their propagation (Butel 2000; Bagga and Bouchard 2014). Many human tumours are linked to viral infections (Dayaram and Marriott 2008; Gatza et al. 2005). In addition to genetic alterations within oncogenes and tumour suppressor genes, virus-induced cancers also arise from the epigenetic cross-talk (Poreba et al. 2011; White et al. 2014b).

Immune modulation and role of cytokines

The T-lymphocytes and B-lymphocytes play vital roles in regulating innate and adaptive immunity. The T-lymphocytes are the primary source of cytokines. While T cells are produced from the bone marrow, their maturation takes place at the thymus. These cells are classified into helper (with CD4 co-receptor), cytotoxic (with CD8 co-receptor), and regulatory (T-Reg) T cells. The helper T cells trigger cytokine production in response to antigens presented by...
MHC Class II and antigen-presenting cells (APCs). These cytokines subsequently trigger B cell differentiation to produce antibodies (Roche and Furuta 2015). In contrast, cytotoxic T cells receive antigens from MHC Class I, become the effector cells, and directly kill the infected cells or cancer cells (Hewitt 2003). The ability of the thymus decreases with age. Therefore, old age appears to be a risk factor for virus infections and cancer (Shaw et al. 2013; White et al. 2014a). The cytokines are glycopeptides and act as humoral regulators at low concentrations (picomolar or nanomolar concentrations), and thus, regulate the host immune response. In gross terms, cytokines induce inflammation in response to tissue injury, infection, or exposure to toxic chemicals (Ashley and Weil 2012) and attract immune cells to the site of injury or infection. A naive T-lymphocyte makes two types of T-helper cells, Th1 and Th2 cells. The Th1 cells facilitate the cell-mediated immune response, whereas Th2 cells facilitate humoral immune response (Mosmann and Coffman 1989). Subsequently, Th17 was identified as another inducer of inflammation (Patel and Kuchroo 2015). Unlike helper T-cells, T-regulatory cells, despite having a CD4 co-receptor on their surface, suppress the inflammatory response. Therefore, in response to mild or nonlethal infections, the T-reg cells will take over the maintenance of immune homeostasis (Fig. 2). However, excessive cytokine production can lead to tissue damage and sepsis. For this reason, cytokine targeting has emerged as an alternate mechanism to intervene in the inflammation (D’Elia et al. 2013).

Between the cytokines, the pro-inflammatory cytokines (IL-1α, IL-1β, IL-2, IL-6, IL-8, IL-11, IL-12, IL-17, IL-18, IL-20, IL-23, IL-33, TNF-α, IFN-γ, BASFF, LIF, OSM, TGF-β, and GM-CSF, and chemokine, MCP-1) produced from Th1 cells and macrophages aggravate the inflammation, whereas the anti-inflammatory cytokines (IL-4, IL-6, IL-10, IL-11, IL-13, EGF, and TNF-β) produced from Th2 cells decreases the inflammation (Dinarello 2007) (Fig. 3). It is interesting to see cytokines such as IL-6 are exhibiting overlapping functions. Th1 cells respond to microorganisms and cancer (Goldszmid et al. 2014), whereas Th2 cells respond to parasite infections (Bourreau et al. 2003). Chemokines are small cytokines produced by normal cells and majorly from the immune cells. Due to their involvement in chemotaxis and cell movement, they function as signalling proteins. Similar to cytokines, chemokines also exhibit pro- and anti-inflammatory responses (Sharma 2015). They are classified based on the number of sulphhydryl groups (S–S) in them, and they are majorly categorised as CXC (CXCL-1, CXCL-2, CXCL-8, CXCL-10, CXCL-12, CXCL-14, CXCL-17) and CC (CCL1, CCL2, CCL3, CCL4, CCL-5) types (Palomino and Marti 2015; Turner et al. 2014) (Fig. 4). Chemokines coordinate with cytokines in an orchestrated manner to regulate the inflammatory responses (Turner et al. 2014; Karin and Wildbaum 2015).

The cytokine response can be inhibited by selective cytokine inhibitors, antibodies against specific cytokines, cytokine receptor antagonists for both membrane and soluble receptors, inhibitors/modulators of cytokine signal transduction, and their transcriptional regulation. Since a cascade of events occurs during the cytokine storm (uncontrolled release of cytokines), the direct cytokine inhibitors, receptor inhibitors, and signal transduction inhibitors have been used to interfere with the cytokine storm. We describe a few commonly used drugs, inhibitors, and drug candidates against cytokine storm in the following sections.

**Viruses and cytokine storm**

Inflammation is a host response to untoward cellular insults and is grossly considered as a host defence mechanism. When an inflammatory response (i.e. cytokine release) occurs in a regulated manner, it is called adaptive. If it happens in an uncontrolled way, it leads to a pathological outcome (Varela et al. 2018). Therefore, the location and variation of cytokine response also can decide the consequences of infection (Noah et al. 2012). Many viral infections can elicit cytokine responses (Tisoncik et al. 2012). Cytokine...
storm is nothing but the overproduction of pro-inflammatory cytokines triggering the hyper-inflammatory response. If the cytokine release is site-specific, it is called local inflammation (i.e. infected cells/tissues and wound/injured site). Unsolicited cytokine production invites immune cells to non-specific sites, thus damaging the unaffected cells/tissues/organs. The cytokines induced in incidences like influenza are considered non-lethal. However, overproduction of these cytokines can also cause severe neuronal damage (Yokota 2003; Ichiyama et al. 2003; Beigel et al. 2005).

**Cancer and cytokine storm**

Cancer emerges from the loss of fine-tuning between the tumour suppressor and oncogenes and epigenetic alterations (Zhu et al. 2015; Kanwal et al. 2015; Blackadar 2016). The host immune system usually takes care of tumour development by inducing inflammatory responses that exhibit anti-tumour activity. In gross terms, the outcome of cancer pathogenesis depends on host immunity (Gonzalez et al. 2018). Further, cancer immunity shown at various developmental stages contributes to the fundamental cancer phenotypes (Hanahan and Weinberg 2011). Additionally, cancer immunity is associated with the compromised immune checkpoints such as programmed cell death protein 1 (PD-1) or its ligand (PD-L1) (Pio et al. 2019). Since cancer inflammation favours carcinogenesis (Balkwill and Mantovani 2001; Germano et al. 2008; Chen and Mellman 2013; Múzès and Sipos 2015), the stage-specific alterations in inflammatory cytokines appear to contribute to immune evasion (Gonzalez et al. 2018). Cytokines promote tumour growth and spread in an autocrine or paracrine manner. The autocrine mechanisms trigger proliferative potential, whereas the paracrine mechanisms initiate cellular transformation and tumour spread (Mantovani 1994; Negus and Balkwill 1996). Various cytokines involved in cancer progression are well-reviewed by Dunlop and Campbell (2000).

**Cytokine storm: cancer versus viral infection**

Several factors, cytokines, interleukins, chemokines, interferons, tumour necrosis factor, and growth factors play a central role in directing the immune cells to reach the target cells (Oppenheim and Fujiwara 1996). However, tumour cells can exhibit low immunogenicity for two reasons, (1)
they arise from the normal cells of the host, and (2) they exist in a heterogeneous population (Vinay et al. 2015). Therefore, it is necessary to trigger a specific or selective antitumour immune response in the host (Chulpanova et al. 2020). Tumour cells can manipulate the host immunity by overexpression of checkpoint molecules such as PD1 and FasL, cytokine suppressors IL-10 and IL-17, and manipulators of tumour microenvironment TGFβ and IL-4, modulation of ligands that bind to MHC molecules, etc. (Pandya et al. 2016). Since cancer emergence is an adaptive response, the chronic inflammation usually observed in tumour cells favours them from targeting self (Singh et al. 2017). Therefore, triggering a specific host immune response is suggested (Blankenstein et al. 2012; Li 2018). The cytokines such as IL-2, IL-12, and TNFα are directly used in anticancer therapies to trigger host immunity (van Horssen et al. 2006; Tugues et al. 2014; Jiang et al. 2016). The use of recombinant oncolytic virus treatments that infects cancer cells and promote cell killing was found to be very promising (Andreansky et al. 1998; Fu et al. 2019). In agreement that viral infections induce an inflammatory response, the engineered oncolytic virus with tumour-specific antigens may also elicit an efficient antitumour response. The limitations imposed by this strategy include tumour heterogeneity, physical barriers in solid tumours, and the impact of the tumour microenvironment (Gulley et al. 2017; Zheng et al. 2019).

SARS-CoV-2 and cytokine storm

The SARS-CoV-2, the severe acute respiratory syndrome coronavirus infection, has been shown to elicit cytokine response on post-viral infection to drive immune cells such as macrophages, NK cells, and dendritic cells to the site of infection, i.e. lungs (Chen et al. 2010). Subsequently, the SARS-CoV-2 that causes coronavirus disease (COVID-19) is also shown to induce a cytokine storm (Song et al. 2020; Ye et al. 2020). The spike protein, S, binds to the angiotensin-converting enzyme 2 (ACE2), which is abundantly expressed in the kidney, heart, lung, and intestine and induces an unwarranted immune response (Kuba et al. 2005; Lan et al. 2020). A few ACE inhibitors with clinical implications are being reviewed by Sweitzer (2003) and suggested to be useful against COVID-19 patients, including patients with hypertension (Hippisley-Cox et al. 2020; Meng et al. 2020). However, it was also indicated that additional data are required to make firm conclusions, and available data should be used with caution for interpretations (Liu et al. 2020a).

Under defective or low immunity, the immune system responds to infection and triggers cytokine production. It could be the reason why cancer patients with low immunity are at risk for COVID-19 (Liang et al. 2020; Lee et al. 2020). The risk assessment was performed based on invasive ventilation, ICU admission, clinical indication, and death between normal versus cancer patients with COVID-19 infection. Although these studies are pertinent to a subpopulation from east Asia (Liang et al. 2020; Liu et al. 2020b), a cohort study that included the USA, Canada, and Spain also suggests that cancer patients are in the high-risk group (Kuderer et al. 2020). However, due to a small sample size or limited demographic data analyses, these correlations did not provide conclusive information (Desai et al. 2020; Wang and Zhang 2020) but provided a possibility that such correlation may be possible.

Since there is an overlap in the potential molecular mechanisms between the inflammatory responses induced by virus infections and autoimmune disorders (Smatti et al. 2019), SARS-CoV-2 disease can also exhibit a similar response. In agreement with this, COVID-19 patients are shown to express autoantibodies to the immunomodulatory molecules that include cytokines (Wang et al. 2020a), potentially leading to autoimmune disorders (Galeotti and Bayry 2020; Mateu-Salat et al. 2020).

Among different cancers, the haematological, lung, and breast cancer patients were reported to be at high risk (Rugge et al. 2020). Interestingly, cancer progression is linked to cytokine-mediated cellular transformation of bystander cells (Drannoff 2004). Nevertheless, the cytokines are being suggested for cancer treatment, indicating that they need to be used in a context-based manner and with precaution (Vilcek and Feldmann 2004; Kim-Schulze et al. 2007; Lee and Margolin 2011; Conlon et al. 2019). Since proinflammatory cytokines negatively influence host immunity against infection, a natural cytokine treatment has both advantages and disadvantages (Rider et al. 2016). The SARS-CoV-2 infection in cancer patients exhibits an aggravated cytokine response, contributing to increased mortality rates (Turnquist et al. 2020; Khalid et al. 2020; Weatherford et al. 2020). Hence, interfering with the cytokine storm appears to be a prerogative response against virus-infected cancer patients.

Inflammation and pain

Inflammation is a dynamic response to tissue injury to clear the damaged tissue or infected cells. Stress is inevitable, and all living beings experience and respond to stress. Pain is a distressing sensation caused by tissue injury, where inflammation triggers pain (Watkins et al. 2003; Zhang and An 2007). Since inflammatory cytokines can trigger tissue damage, they will have a more significant impact in triggering the host’s pain response at different locations (Navarra et al. 1991; Lyson et al. 1991; Leonard 2015; Muley et al. 2016). The SARS-CoV-2 infection also can cause pain in distant locations than the primary infected sites (Acharya et al. 2020).
Various receptors, such as opioids, vanilloid, capsaicin, are implicated in pain response (Tominaga and Julius 2000; Caterina and Julius 2001; Pathan and Williams 2012). Interestingly, the respiratory viruses can also induce intracellular pain receptors and persuade pain in response to tissue damage (Omar et al. 2017). Since SARS-CoV-2 infection is also a respiratory infection, the involvement of pain receptors during virus infections can also be considered for treating pain.

The cyclooxygenases (COX enzymes) are implicated in pain response. Between the two major COX enzymes, COX-1 functions constitutively to maintain tissue homeostasis, whereas COX-2 is involved in inflammation and pain (Williams et al. 1999; Deeb et al. 2008). COX-2 contributes to cancer progression by inducing the pro-inflammatory cytokines, however, suppressing the host immunity. It could be why COX-2 has become a pharmacological target against cancer (Liu et al. 2015; Hashemi Goradel et al. 2019; Table 1). Like in cancer inflammation, SARS-CoV-2 infection also triggers the transcription of COX-2, indicating its involvement in the disease outcome (Liu et al. 2007; Das 2020). The lipoxygenases are lipid mediators and are involved in producing the leukotrienes, which act as chemotactic agents for immune cells (Peters-Golden and Henderson 2007). In the case of SARS-CoV-2 infection, leukotrienes are not paid attention to (Funk and Ardakani 2020). Since leukotriene inhibitors are used in anti-cancer treatments (Steele et al. 1999; Werz and Steinmiller 2006), they are also suggested for COVID-19 patients (Citron et al. 2020; Funk and Ardakani 2020). However, it has been recommended that ACE inhibitors in combination with NSAIDs increase the risk of kidney injury, yet, sufficient scientific evidence has not been established for this (Zolk et al. 2020).

### Table 1 A few known NSAIDS as COX inhibitors

| Drug candidate | Physiological effects | Inhibits |
|----------------|-----------------------|----------|
| Aspirin        | Anti-inflammatory, analgesic, and antipyretic | COX-1    |
| Celecoxib      | Anti-inflammatory     | COX-2    |
| Diclofenac     | Anti-inflammatory and analgesic | COX-1/2 |
| Etodolac       | Anti-inflammatory     | COX-2    |
| Etorocoxib     | Anti-inflammatory, analgesic, and antipyretic | COX-2 |
| Fenoprofen     | Anti-inflammatory, analgesic, and antipyretic | COX-1/2 |
| Flurbiprofen   | Anti-inflammatory, anti-miotic, and antipyretic | COX-1/2 |
| Ibuprofen      | Anti-inflammatory, analgesic, and antipyretic | COX-1/2 |
| Indomethacin   | Anti-inflammatory, analgesic, and antipyretic | COX-1/2 |
| Ketoprofen     | Anti-inflammatory, analgesic, and antipyretic | COX-1/2 |
| Ketorolac      | Anti-inflammatory and analgesic | COX-1/2 |
| Meclofenamate  | Anti-inflammatory and analgesic | COX-1/2 |
| Mefanamic acid | Anti-inflammatory and analgesic | COX-1/2 |
| Meloxicam      | Anti-inflammatory and analgesic | COX-2 |
| Nabumetone     | Anti-inflammatory     | COX-1/2 |
| Naproxen       | Anti-inflammatory, analgesic, and antipyretic | COX-1/2 |
| Oxaprozin      | Anti-inflammatory and analgesic | COX-1/2 |
| Piroxicam      | Anti-inflammatory     | COX-1/2 |
| Sulindac       | Anti-inflammatory     | COX-1/2 |
| Tolmetin       | Anti-inflammatory and analgesic | COX-1/2 |

The inflammatory signal transduction involves pattern recognition receptors (PRRs) both on the cell surface and in the cytoplasm. The primary role of PRRs is to respond to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs); where the former are associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs); while the latter one is related to infection, the latter one emerges from the host response (Bianchi 2007; Newton and Dixit 2012). Since the influenza virus shares homology with SARS-CoV-2, there may be an overlap of inflammatory signal transduction pathways. Similar to spike protein, PAMPs also recognise ACE-2 receptors and activate toll-like receptors (TLRs). These TLRs spanning the plasma membrane have cytosolic adaptors, which activate transcription factors such as NF-kB, AP1, CREB, IRF, etc. It is also interesting to note that some of the mitogen-activated protein kinase (MAPK) members are also involved in such signalling events. Since mitogen signal transduction is vital for host cell survival, MAPK inhibitors cannot be used for infection-induced inflammation (Catanzaro et al. 2020). However, the MyD88, which is upstream of MAPK, can act as an adaptor for TLR; thus, it appears to be one such target (Kawasaki and Kawai 2014). It could be why the signal transduction pathways leading to cytokine production have become attractive targets for anti-inflammatory therapeutics. A review by Gao et al. (2017) summarises some of the TLR inhibitors in the application front for treatment.

Among several cytokine receptors associated with disease pathology, type I and type II superfamily are linked with Janus Kinases (JAKs). Since JAK1/2 responds to multiple cytokine receptors, targeting JAKs with conventional kinase inhibitors is proposed to interfere with the inflammatory responses (Schwartz et al. 2017). The signal activator and transducer (STAT) transcriptional factors are activated in response to JAK signalling. Therefore, the JAK-STAT signalling pathway has become an attractive target for interfering with inflammation. Interestingly, the STAT protein activation serves a dual role: (1) to trigger inflammation in response to cytokine binding to its receptor and
(2) to suppress cytokine response. For this reason, only JAK inhibitors are used against inflammation (Yoshimura et al. 2003) (Fig. 5). Hence, several JAK inhibitors such as ruxolitinib, baricitinib, fedratinib, olacitinib, tofacitinib, solcitinib, filgotinib, upadacitinib, decernotinib, PF-06651600, etc. can be examined against COVID-19 (O’Shea et al. 2013; Schwartz et al. 2017; Seif et al. 2020; Table 2). Towards this, NIH News Release indicated a randomised, controlled clinical trial of the JAK inhibitor baricitinib for COVID-19 treatment. Similarly, the JAK inhibitors such as ruxolitinib combined with eculizumab are effective against SARS-CoV-2 (Giudice et al. 2020).

The c-jun N-terminal kinase (JNK) stress signalling pathway is also implicated in cancer progression. However, this kinase exhibits a dual role both as an oncogene and tumour suppressor (Tournier 2013). The JNK pathway modulates cell death pathways in infectious bronchitis virus (IBV) virus infection suggests that it contributes to disease pathogenicity (Fung and Liu 2017). Interestingly, it has been shown that the JNK pathway contributes to SARS-CoV-2 pathogenesis (Mizutani 2009; Mizutani et al. 2005; Singh et al. 2020). An updated list of selective JNK inhibitors suggests that they can be used against infection and stress-activated stress signalling like cancer (Wu et al. 2020a). No significant findings were made linking JNK pathways with SARS-CoV-2 infection, which may need to be examined. Like JNK, non-receptor tyrosine kinase 2 (Tyk2) is implicated in cancer progression (Wöss et al. 2019; Fig. 5). Tyk2 has already been identified as a target for viral pneumonia (Berg et al. 2017). Therefore, the available Tyk2 inhibitors (Table 2) can be examined against SARS-CoV-2 induced inflammatory signal transduction.

![Common signal transduction pathways triggered by cytokines](image)

**Table 2** A few known kinase inhibitors

| Drug candidate | Molecular target |
|----------------|------------------|
| Baricitinib    | JAK1/2/3         |
| BMS-986165     | Tyk2             |
| Decernotinib   | JAK-3            |
| Delgocitinib   | pan inhibitor of JAKs |
| Fedratinib     | JAK-2            |
| Filgotinib     | JAK-1            |
| Itacitinib     | JAK-1            |
| NDI-031232     | Tyk2             |
| NDI-031407     | Tyk2             |
| Olacitinib     | JAK1/2/3         |
| Peficitinib    | JAK-1/2/3        |
| PF-06651600    | JAK-3            |
| PF-06826647    | Tyk2/JAK-1/2     |
| Ruxolitinib    | JAK1/2           |
| SAR-20347      | Tyk2/JAK-1/2/3   |
| Solcitinib     | JAK-1            |
| Tofacitinib    | JAK1/3           |
| Upadacitinib   | JAK-1            |

**The overlapping functions of cytokine storm in cancer and SARS-CoV-2 infections**

Inflammation has been identified as a facilitator of tumour progression (Philip et al. 2004; Lu et al. 2006). However, in the case of SARS-CoV-2 infections, although the clinical features correlate with influenza (Liu et al. 2016), the serum levels of IL-2 and IL-6 were suggested to act as prognostic markers (Chen et al. 2010). Subsequent studies have indicated how cytokine storm leads to pathological outcome (Zhou et al. 2020a). Although there are suggested treatment regimens to interfere with cytokine storm (Schulert and Grom 2015), inducing the anti-inflammatory responses by triggering a specific transcriptional response was found to be effective (Brun-Buisson et al. 2011). Subsequently, several drugs and inhibitors are effective against cytokine storm, including statins, antioxidants, anti-immunoglobulin injections, COX-2 inhibitors, and anti-TNF agents, etc. (Holdsworth and Gan 2015; Liu et al. 2016; Wang et al. 2020b; Liu and Ying 2020).
After the SARS-CoV-2 infection, during COVID-19 disease, the first stage shows high viral load and fewer symptoms on 1–2 weeks of post-viral infection (Zhou et al. 2020b). In contrast, the second stage shows increased cytokine storm and organ failure and may last for weeks (Guo et al. 2020). The primary target of SARS-CoV-2 is the ACE-2 receptors in the lung epithelium (Kuba et al. 2005; Lan et al. 2020). Pro-inflammatory cytokine involvement and their effective inhibition using tocilizumab, myoinositol, azithromycin, chloroquine, certolizumab, etc. were suggested (Costela-Ruiz et al. 2020; Cortegiani et al. 2020). The cytokine response, therefore, also acts as an indicator of viral load and disease severity. Since there are no universal cytokine response signalling patterns that work in a disease or infection-specific manner, drugs that inhibit inflammatory cytokines in cancer and other conditions may work against COVID-19 (Luo et al. 2020). Based on the literature survey, it is possible to repurpose anticancer and anti-inflammatory drugs to lower the cytokine overload in COVID-19 (Fig. 6).

Anticancer drugs can induce immunosuppression; therefore, loss of tumour growth at the primary location does not always signify decreased tumour load in response to chemotherapy. A decrease in tumour growth at the primary location could also signify enhanced or acquired metastatic potential of tumour cells (Penn 1975). Since conventional chemotheraphy fails to intervene with the unwarranted cytokine response, combined immunotherapy with chemotherapy has emerged as a novel strategy to combat cancer (Vanneman and Dranoff 2012). Among the modulators of cancer immunity, the checkpoint inhibitors, PD-1 and its ligand PD-L1, and CTLA-4 can be targeted by chemical entities or monoclonal antibodies (Rotte 2019). Similarly, chimeric antigen receptor (CAR)-T cell therapy and oncolytic virus infections are also useful (Guedan and Alemany 2018). There is a long list of anti-inflammatory drugs used against cancers, which may not directly elicit anticancer properties but are efficient against the cytokine storm and sensitise tumour cells to conventional chemotherapeutic drugs (Rayburn et al. 2009; Zappavigna et al. 2020).

Since anticancer drugs or drugs used against cancer inflammation can also intervene with the cytokine storm induced by the SARS-CoV-2 virus, the scope of using these drugs against COVID19 is encouraging (Saini et al. 2020; Ciliberto et al. 2020; Hu et al. 2020). Among the three significant steps considered to target any viral infections, preventing virus entry into the host, interfering with the virus replication in the host, and interfering with the unwarranted immune response appeared to be critical (Stebbing et al. 2020; Cheng et al. 2020). Further, the classical antiviral drugs such as remdesivir can interfere with RNA-dependant RNA polymerase functions (Beigel et al. 2020) may not address the concerns raised by the cytokine storm. Therefore, repurposing the drugs used against cancer inflammation can be examined against SARS-CoV-2 infection as a complementary therapy.

**Potential inhibitors of cytokine storm in the context of SARS-CoV-2**

**BCG vaccine**

BCG is a freeze preparation containing live bacteria derived from an attenuated strain of mycobacterium bovis known as *Bacillus of Calmette and Guerin* and used against tuberculosis. BCG is ineffective against HIV infections wherein there is an extensive immunosuppression reported (Dheda et al. 2017). Similar to SARS-CoV-2, *Mycobacterium* infection also triggers innate immune responses (Cooper and Khader 2008). Therefore, the BCG vaccine is thought to sensitize the host system against COVID-19 (Escobar et al. 2019; Arlehamm et al. 2020; O’Neill and Netea 2020). Although BCG was speculated to intervene SARS-CoV-2 related inflammatory response, sufficient scientifically approved data could not be obtained to strengthen this. Further, no strong correlation could be drawn from the available epidemiological data sets between BCG vaccination and SARS-CoV-2 infection.
Bordetella Pertussis

*Bordetella Pertussis* is a gram-negative bacterium whose infection causes whooping cough and severe respiratory malfunctions leading to bronchopneumonia and encephalopathy. The severity and the outcome of the disease depend on the host’s innate immunity. Heat killed bacterium is used as a vaccine to reduce the cytokine storm (Li et al. 2010) and could be the reason why it was suggested for COVID-19 (Alkholy et al. 2020). The World Health Organization (WHO), in a recent report on Mythblasters, has indicated that vaccines against pneumonia will not protect individuals from COVID-19 since scientific evidence to support such claims is lacking (Convertino et al. 2020).

Sepsis

Sepsis is a systematic response to organ dysfunction induced by infection. Overproduction of cytokines results in sepsis (Rittirsch et al. 2008; Boomer et al. 2011). Sepsis-induced organ dysfunction in COVID-19 patients has been reported (Lin 2020). Blood being the primary carrier for cytokine distribution to various tissues in the body, hemoperfusion has been suggested for severe sepsis/lung injury as reviewed (Chaudhry et al. 2013; Schädler et al. 2013). However, neither scientific nor clinical data relevant to hemoperfusion and SARS-CoV-2 infections are available (Li et al. 2020a). Interestingly, the use of plasma from the COVID-19 recovered patients is effective against SARS-CoV-2 infection but was broadly thought to come from the antibody-mediated virus inhibition (Yiğenoğlu et al. 2020; Sedokani and Feizollahzadeh 2020; Farhat et al. 2020). However, more conclusive data are needed to confirm these findings.

Azathioprine

Azathioprine acts as an immune modulator to suppress the host response (Fuss et al. 1999; Yeo et al. 2019). Therefore, it is grossly used to prevent graft rejection during organ transplantation and inhibits inflammation during rheumatoid arthritis (Rodrígues-Perálvarez et al. 2014; Suarez-Almazor et al. 2000). Due to its immunosuppressant activity, it is suggested to be used against the cytokine storm in respiratory distress, however, in combination treatments (Vaz et al. 2011; Shorr et al. 2003; Wu et al. 2020b). Azithromycin is now shown to reduce the viral load in early SARS-CoV-2 infection either alone or in combination with chloroquine (Rajaiah et al. 2020; Lagier et al. 2020).

Methotrexate

Methotrexate was initially used to slow down cancer cell growth and subsequently showed to exhibit immune-suppressant activity. Methotrexate is effective against COVID-19 induced cytokine production alone or with JAK1/2 inhibitors (Khan and Durairaj 2020). Since it works against arthritis to reduce inflammation, it is being suggested for COVID-19 (Frohman et al. 2020; Rajaiah et al. 2020).

Glucocorticoids

Glucocorticoids are produced by the adrenal glands and are known to suppress the immune responses by inhibiting inflammation and activating pro-inflammatory responses (Fantuzzi and Ghezzi 1993; Schwiebert et al. 1996). Since glucocorticoid receptor stabilisation and ligand–receptor interactions are regulated by the molecular chaperone Hsp90, interfering with the chaperoning functions of Hsp90 is also implicated in interfering with the cytokine inhibitory response (Morishima et al. 2018). Considering their anti-inflammatory response, treating COVID-19 patients with corticosteroid drugs was strongly suggested (Cook et al. 2015; RECOVERY Collaborative Group et al. 2020; Johnson and Vinetz 2020). The corticosteroids are widely used against SARS and MERS, and for COVID-19 treatment, they were already used at the clinic and shown to have beneficial outcomes (Zha et al. 2019).

Monoclonal antibodies

There are now a few approved vaccine or vaccine candidates against COVID-19 that include antibodies. The available monoclonal antibodies aim to spike glycoproteins on SARS-CoV-2 and interfere with the virus’s host cell entry (Marovich et al. 2020; Shanmugaraj et al. 2020; Sewell et al. 2020). However, it is suggested that antibodies against the conformationally altered T-lymphocytes and their receptors can more efficiently decrease the circulating lymphocytes and the cytokine storm (Hu et al. 2020). Therefore, research towards developing specific monoclonal antibodies against cytokines and their respective receptors may be effective against the cytokine storm.

C-reactive protein

The C-reactive protein (CRP) levels in the blood acts as an indicator for inflammation. Since increased CRP appears to decrease cytokine levels, they are implicated in anti-cytokine response (Mallya et al. 1982; Pradhan et al. 2001) and suggested for the risk assessment during COVID-19 (Sahu et al. 2020; Wang et al. 2020c; Yang et al. 2020b). Interestingly, few anti-inflammatory drugs that are shown to reduce CRP levels (Prasad 2006; Zhang et al. 2016) are associated with COVID-19 (Zhang et al. 2020a). Ulinastatin has effectively reduced serum CRP levels and systemic inflammation.
Therefore, this drug is suggested for COVID-19 as an adjuvant treatment (Dixit et al. 2020).

**Anti pain/analgesic drugs**

Opioid agonists such as tramadol, codeine, morphine, etc. are considered the most potent pain killers. Non-opioid agonists such as paracetamol, ibuprofen, aspirin, etc. are used against chronic pain. The opioid pain killers interfere with membrane receptors, and the non-opioid pain killers interfere with metabolic pathways (Graham and Scott 2005; Orlando et al. 2015). Both opioid and non-opioid drugs have been suggested for COVID-19 patients (Rinott et al. 2020; Shanthanna et al. 2020) for pain management (El-Tallawy et al. 2020). However, opioid overdose leads to compromised immune functions. It could be the reason why individuals with opioid addiction are considered to be at high risk for COVID-19 (Dubey et al. 2020).

**Anti-inflammatory drugs: cancer versus COVID-19**

The inflammatory cytokines from cancer cells can promote the neoplastic transformation of bystander cells. Therefore, interfering with inflammatory responses impede cancer spread and progression (Hofseth and Ying 2006; Arias et al. 2007). In addition to chemotherapeutic drugs that can promote cytotoxicity in target cells, hormonal therapy or steroid therapy has emerged as an alternate strategy to treat cancer. The hormonal therapy is effective against hormone-responsive tumour cells from the breast and endometrium in females and prostate in males. Interestingly, several drugs that interfere with hormone regulatory pathways are known to interfere with inflammatory responses (Sereda and Werth 2006; Leggas et al. 2009). Nonsteroidal anti-inflammatory drugs are being used against cancer to reduce tumour inflammation (Thun et al. 2002; Kim-Schulze et al. 2007). Among commonly used antitumour inflammatory drugs, COX and LOX inhibitors have gained much attention (Rayburn et al. 2009). However, corticosteroids and commonly used analgesic drugs like aspirin and ibuprofen are also shown to interfere with cancer inflammation. These studies reiterate the potential of repurposing anti-inflammatory and anticancer drugs against COVID-19. Since cancer patients exhibit a two-fold increased risk of COVID infection than healthy individuals, these drugs can be considered.

The intriguing findings indicated that SARS-CoV-2 infection could promote chemoresistance and thus, challenges current anticancer treatments (Vatansy et al. 2020). It suggests the impact of SARS-CoV-2 infection in cancer patients who are on chemotherapy. While the acquired multidrug resistance itself is challenging the cancer treatments (Nikolaou et al. 2018; Vasan et al. 2019; Ward et al. 2020), the virus-induced drug resistance probably leads to adverse consequences, which may hamper recovery from cancer. Further, cancer and SARS-CoV-2 infection can trigger similar or overlapping inflammatory responses. Hence, immune modulation is primarily suggested for the prophylaxis of COVID-19 (Mohamed-Hussein et al. 2020). On the other hand, the anticancer drug ibrutinib, a tyrosine kinase inhibitor, reduces lung inflammation (Florence et al. 2018) and is suggested for COVID-19 (Treon et al. 2020). Several anticancer drugs that can be tested against the complications induced by COVID-19 are already reported (Saini et al. 2020). Several IL-6 inhibitors (Farooqi et al. 2020; Uciechowski and Dempke 2020) and TNF inhibitors (Sedger and McDermott 2014) are suggested to interfere with inflammation induced by COVID-19 (Table 3).

**Hydroxychloroquine, azithromycin, and zinc**

The quinone isolated from the cinchona tree is widely used against malarial fever (Ben-Zvi et al. 2012). Subsequently, it is used against various ailments, including antiviral treatments (Al-Bari 2015). Hydroxychloroquine has been shown to enhance anticancer drug effect (Li et al. 2018a; Wang et al. 2019). Interestingly, quinone is effective against chronic inflammation (Li et al. 2018b). The inhibitory effects of hydroxychloroquine against SARS-CoV-2 were promising (Vincent et al. 2005; Yao et al. 2020). Azithromycin, an antibacterial drug, is shown to potentiate the antiviral effects of chloroquine in Plasmodium infection (Sagara et al. 2014) and is subsequently shown to reduce SARS-CoV-2 viral load (Lagier et al. 2020). Chloroquine acts as a zinc ionophore and thus facilitates zinc accumulation (Xue et al. 2014) and potentiates antiviral immune response (Read et al. 2019). It could be the reason why azithromycin and zinc combination with chloroquine has been recommended for the high-risk COVID-19 patients (Derwand and Scholz 2020). Although

| Drug candidate | Target cytokine |
|----------------|----------------|
| Adalimumab     | TNF            |
| Anifrolumab    | IFN            |
| Certolizumab   | TNF            |
| Clazakizumab   | IL-6           |
| Emapalumab     | IFN            |
| Etanercept     | TNF            |
| Golimumab      | TNF            |
| Infliximab     | TNF            |
| Olokizumab     | IL-6           |
| Sarilumab      | IL-6R          |
| Siltuximab     | IL-6           |
| Tocilizumab    | IL-6           |
the initial non-randomised trials with chloroquine and azithromycin were promising (Gautret et al. 2020), combining them with the antiviral drug remdesivir (Risch 2020) and ivermectin (Caly et al. 2020; Sharun et al. 2020) is found to be more effective. A cohort study from the United States of America further strengthens the hypothesis that hydroxychloroquine decreases the mortality associated with the SARS-CoV-2 infection (Gentry et al. 2020). Although some prophylactic role for hydroxychloroquine has been discussed in selected geographical locations (Rathi et al. 2020; Nina and Dash 2020; Mégarbane and Scherrmann 2020; Principi and Esposito 2020), more demographic data sets are needed to conclude.

Examples and mechanisms of action of anti-inflammatory agents against SARS-CoV-2 and cancer

We discussed how anti-inflammatory and anti-cancer drugs exhibit their potential to work against SARS-CoV-2 infection in earlier sections. In this section, we discuss how these drugs work in cancer patients after SARS-CoV-2 infection. The cancer patients with low immunity defence are more prone to SARS-CoV-2 infection. Under these circumstances, any medication used against cancer should also work against viral infection without compromising the immune system. Otherwise, the motive of repurposing anticancer drugs for COVID-19 treatment cannot be achieved (Allegra et al. 2020).

Glucocorticoids: implications and limitations, cancer versus COVID-19

Unlike sex hormones, progesterone and estrogen, which are also implicated in cancer progression, glucocorticoids act as immunosuppressants and are extensively used for organ transplants (Curtis 2006; Buxant et al. 2010; Pufall 2015; De Lucena and Rangel 2018). The glucocorticoid binding to its receptor can trigger apoptosis in the host cell. Therefore, it is considered an anticancer agent both in haematological and solid tumours (Greenstein et al. 2002; Keith 2008). Glucocorticoids can also exhibit differential responses in different cancer cells (Lin and Wang 2016). Nevertheless, they are considered for treating inflammation (Vandewalle et al. 2018). These studies have indicated that they work against all cancers as anticancer agents by triggering anti-inflammatory gene transcription. The chronic use of glucocorticoids can lead to prolonged immunosuppression, which may facilitate novel infections to occur. Therefore, the use of glucocorticoids should be used with caution (Klein et al. 2001).

Glucocorticoids are even suggested for SARS and COVID-19 treatment to reduce inflammation (Cinatl Jr et al. 2005; Xiang et al. 2020). However, since high doses are recommended for acute respiratory infections, prolonged use may lead to opportunistic infections in the background of immune suppression (Klein et al. 2001; Cinatl Jr et al. 2005; Lossignol 2016; Yang et al. 2020a). Since cancer patients are in the high-risk group for COVID-19, addressing SARS-CoV-2 induced inflammation alone with high doses of glucocorticoids can lower host immunity and thus, can aggravate both cancer and virus spread and can invite other infections to occur in cancer patients (Slimano et al. 2020; Hanna et al. 2020; Russell et al. 2020; Table 4). Inducing anti-inflammatory response using moderate doses of glucocorticoids, therefore, appeared to decrease COVID-19 associated mortality.

COVID-19 impact on opportunistic diseases in S. Asia and Sub-Saharan Africa

After identifying novel coronavirus pneumonia as coronavirus disease, COVID-19 (Jiang et al. 2020), it was found that comorbidities associated with the virus infection may have a more significant impact on the disease outcome (Wang et al. 2020d). Therefore, it was suggested that a thorough evaluation is necessary to understand the actual cause of mortality. While the COVID-19 susceptibility is ascribed to elderly individuals, several factors such as gender, nutrition, and natural immunity need to be considered for appropriate assessment of the disease susceptibility and pathological outcome. The high-calorie diet contributing to obesity and type 2 diabetes is regarded as one of the risk factors for the COVID-19 associated mortality (Butler and Barrientos 2020). Targeting ACE2 receptors that contribute to SARS-CoV-2 infection can cause cardiac dysfunction (Babapoor-Farokhran et al. 2020). Some antiviral drugs have had a negative impact on cardiac functions (Zheng et al. 2020). Therefore, patients with cardiovascular diseases can also fall under high-risk groups for infection. Men

| Drug candidate     | Physiological effect                      |
|--------------------|------------------------------------------|
| Beclomethasone     | Anti-inflammatory                        |
| Betamethasone      | Anti-inflammatory                        |
| Budesonide         | Anti-inflammatory                        |
| Dexamethasone      | Anti-inflammatory and analgesic          |
| Fludrocortisone    | Anti-inflammatory                        |
| Hydrocortisone     | Anti-inflammatory                        |
| Methyl Prednisolone| Anti-inflammatory and immunosuppressive  |
| Prednisone         | Anti-inflammatory                        |
| Prednisolone       | Anti-inflammatory and anti-cancer        |
| Triamcinolone      | Anti-inflammatory                        |
over women are more vulnerable to the infection, suggesting hormonal regulation and natural immunity impact the condition (Agrawal et al. 2020). Surprisingly, the immune-mediated complement activation also contributes to the pathology of coronavirus infection (Gralinski et al. 2018). Therefore, it is viewed that innate immunity can aggravate the disease (Birra et al. 2020), whereas adaptive immunity can facilitate virus clearance (Paces et al. 2020). Since cellular immunity plays a crucial role in producing neutralising antibodies (Poonia and Kottilil 2020), understanding the immune correlations with host immunity appears essential.

An exciting intervention was made based on viral infection patterns in some parts of the world that immune cross-reactivity protects patients from COVID-19 impact (Reche 2020). However, the explanation given for this was based on available epitope information from common viruses: those infected at different stages of adult life such as Herpes Simplex (HSV), Hepatitis B (HBV), Influenza B (IBV), Papilloma (PaV), Epstein–Barr Virus (EBV), Human Cytomegalovirus (HCMV), Human Rhinovirus (HRV), Human Immunodeficiency Virus (HIV), etc. More interestingly, the interpretation was also made on early childhood vaccinations against Mumps Virus (MuV), Rubella Virus (RuV), Measles Virus (MeV), and more. Although the suggested immune reactivity or immune responses between children and adults are different, childhood vaccinations appear to play a role against SARS-CoV-2 infection (Beric-Stojsic et al. 2020; O’Neill and Netea 2020). Further, it is hypothesised that vaccinations from other viruses can prepare the immune system for subsequent infections (Letto 2020).

Malaria has been a more significant risk factor for some Asian countries and majorly sub-Saharan Africa (WHO 2019). Malaria can also induce cytokine storm. Hence antimalarial drugs may be effective against inflammation induced during COVID-19 (Gutman et al. 2020). It has been reviewed in previous sections how antimalarial drugs can work against COVID-19. However, due to lockdown restrictions and poor economic conditions, several primary health care measures have been impacted, in turn impacting malaria and COVID-19 associated recovery (Zawawi et al. 2020; Meo et al. 2020). The lessons learned from the Ebola virus outbreak on malarial treatment warns us to avoid a similar situation during the COVID-19 pandemic (Walker et al. 2015; Paintsil 2020). Similarly, health care measures against cardiovascular diseases also need to be paid attention to (Lukhna et al. 2020). A study also analyses how low- and middle-income countries, including Africa, are affected by the COVID-19 pandemic with HIV and tuberculosis, in addition to malaria (Hogan et al. 2020).

**High rates of malignancies caused by infectious agents with relatively low rates of COVID-19**

In earlier sections, we discussed that cancer patients are vulnerable to SARS-CoV-2 infections due to their low immunity from cancer itself or immunosuppressant chemotherapeutic interventions (Cannizzaro and Puglisi 2020). It reiterates that cancer patients are at high risk of COVID-19. In one of the early cohort studies, it was found that a significant number of COVID-positive individuals are cancer patients (Liang et al. 2020). The anoxic hypoxia upon SARS-CoV-2 infection is one of the causes of hepatitis and liver damage (Sun et al. 2020). Besides, acute hepatitis has been reported to occur before respiratory complications suggesting vulnerability of hepatitis patients to the COVID-19 risk and hepatocellular carcinoma (Wander et al. 2020; Wingrove et al. 2020). On the other hand, human papillomavirus (HPV) infections contribute to nearly 5% of human cancers and influence cancer immunotherapies (Castellsagué et al. 2017; Zhou et al. 2019). Cervical cancer caused by HPV majorly affects women compared to men (Bray et al. 2018). However, it is reported that due to the presence of ACE-2 receptors on all testicular cells, similar to SARS-CoV-1 that causes male infertility, SARS-CoV-2 is expected to affect the spermatogenesis (Vishvkarma and Rajender 2020; Batihra et al. 2020). Since cancer patients receiving chemotherapy are at high risk for COVID-19 disease due to immunosuppression, additional care is required for such patients (Zhang et al. 2020a, b; Dewan et al. 2020).

Kaposi’s sarcoma herpesvirus/human herpesvirus 8 (KSHV/HHV8) infections can be primarily associated with low-grade cancers. However, they were also observed with endemic viral infections such as HIV (Radu and Pantanowitz 2013). It has been proposed that SARS-CoV-2 infections can enhance the oncolytic activity of the herpes virus, and thus contribute to disease morbidity (Chen et al. 2020a). HIV patients with compromised immune systems are at high risk of COVID-19 disease as HIV infection not only compromises the immune responses but also associates with cancer incidences (Ji and Lu 2017; Shiau et al. 2020). Considering the abundance of ACE2 receptors in the gastrointestinal tissues (Harmer et al. 2002), it has been shown that SARS-CoV-2 can affect the gastrointestinal system (Xiao et al. 2020). Since the gastric acids do not inactivate the virus, it is presumed that people affected with *Helicobacter pylori* (*H. pylori*) and those suffering from gastritis are more prone to SARS-CoV-2 infection (Uno 2020). These data suggest that aged individuals with cancer-associated viral infections such as HIV, HPV, and KSHV/KSHV8 and bacterial infections such as *H. pylori* are at high risk.
Summary and perspectives

Triggering the immune responses against foreign bodies, chemicals, toxins, and microorganisms is a natural phenomenon of all living beings. At the same time, excessive stimulation of immune molecules elicits tissue damage and can lead to mortality. Lowering the inflammatory responses can minimise such damage and contribute to survival. The chronic inflammation observed in cancer incidences is beneficial for the spread of disease and will not result in rapid tissue damage or organ failure. However, certain anti-inflammatory drugs are shown to lower cancer incidences as they interfere with cancer growth and spread. The microorganism infections also trigger the host inflammatory response. Since the rate of proliferation and spread of microorganisms is inexhaustible, it can lead to acute inflammation and tissue damage. A set of pro-inflammatory cytokines aggravates the inflammation. Therefore, lowering or interfering with the uncontrolled synthesis of pro-inflammatory cytokines may reduce tissue damage or organ failure. An increase in anti-inflammatory cytokines that are counterproductive to the pro-inflammatory cytokines is necessary in immunological perseverance.

The inflammation associated with viral infection, in particular, respiratory disease, is a challenge to clinicians and researchers. The actual question arises as to which one to target first, the inflammation or infection. Although decreasing the viral load remains to be a prerequisite, the damage caused by acute inflammation warns that the inflammation should be addressed first. Since conventional anti-inflammatory drugs are just good enough to reduce the inflammatory responses, they are usually combined with antiviral drugs. Therefore, lowering the inflammatory response either alone or with antiviral drugs appears to be beneficial. In the COVID-19 disease, the increase in viral load or triggered cytokine storm is always unpredictable. There is no specific incubation period for individuals, and it can occur together. Therefore, the mortality rates associated with inflammation or cytokine storm are relatively high compared to the virus load itself. The life-saving approach suggested is to lower the inflammation either alone or in combination with antiviral drugs. Developing new antiviral drugs and their novel combinations is not feasible since studies related to the basic understanding of the SARS-CoV-2 virus are still on, which is due to high mutation rate or unpredictable patterns of infection (van Dorp et al. 2020; Chen et al. 2020b; Li et al. 2020b). The immediate available option is to repurpose available anticancer anti-inflammatory drugs against COVID-19 associated inflammation. The comprehensive coverage of known anti-inflammatory agents already in the clinical trials against cancer has been reviewed in earlier sections (Di Lorenzo et al. 2020; Gougis et al. 2020). The advantages and consequences of using such drugs in the clinic are discussed in this review in detail.

COVID-19 pandemic is rapidly spreading through all nations, and in some parts, confronting in waves. Though there are differences of opinion in using anti-inflammatory and anticancer drugs against COVID-19, the success stories reiterate that they are beneficial in lowering the mortality rates. Since several such studies are still in the clinical level, in due course of time, with appropriate demographic, disease severity versus mortality, with and without anti-inflammatory drugs, they may provide conclusive and confirmative information. The repurposing of drugs such as chloroquine, non-steroidal anti-inflammatory drugs, glucocorticoids, etc. are promising for COVID-19 either alone or in combination. However, these drugs should be used with caution since prolonged suppression of the immune system can invite other opportunistic infections to occur. A particular window period and a moderate dose but not higher amounts are being suggested (Russell et al. 2020). Based on the available information, we propose how low, medium, and increased cytokine storm responses can be modulated by glucocorticoids (Fig. 7).

It is known that individuals with autoimmune disorders are more prone to cancer, where compromised immune responses act in favor of cancer (Giat et al. 2017). SARS-CoV-2 has been shown to induce autoimmunity (Halpert and Shoenfeld 2020; Ehrenfeld et al. 2020), which may invite opportunistic diseases such as cancer with long-lasting complications even with decreased viral load. Therefore, countering the inflammatory storm should be prioritised while subsequent treatments are directed to reduce the viral load or spread. Accordingly, similar to cancer patients, the patients with autoimmune disorders can also be considered as high-risk groups (Lagadinou et al. 2020) and may need anti-inflammatory drug treatments, however, in a case-specific manner.
Fig. 7 A proposed hypothesis of anti-inflammatory drugs for cancer patients infected with SARS-CoV-2. The effect of glucocorticoid treatment against SARS-CoV-2 induced cytokine storm in low- and high-level infection versus cancer patients is described. The glucocorticoid treatment can compromise the cytokine storm from both low- and high-level infection, probably leading to no or decreased mortality rates and thus, patient recovery. The glucocorticoid treatment appears to compromise high-level infection in cancer patients; however, it can lead to secondary infections due to low or compromised immune responses, resulting in increased mortality rates. Since cancer patients infected with SARS-CoV-2 may not respond to lower doses of anti-inflammatory drugs, increasing the drug dose can invite other opportunistic infections to occur. Therefore, the predicted strategy advises the systematic and context-based use of glucocorticoids for the treatment of cancer patients infected with SARS-CoV-2.

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Declaration

Conflict of Interest The author declares no conflict of interest.

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