JAK-STAT signaling as an ARDS therapeutic target: status and future trends

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Abstract

Acute respiratory distress syndrome (ARDS) is an acute respiratory disease which is characterized by non-cardiogenic pulmonary oedema. It has a high mortality rate and lacks effective pharmacotherapy. As the outbreak of COVID worldwide, the mortality of ARDS has increased correspondingly, which makes it urgent to find effective targets and strategies for the treatment of ARDS. Recent clinical trials of Janus kinase (JAK) inhibitors in treating COVID induced ARDS have shown a positive outcome, which makes the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway a potential therapeutic target for treating ARDS. Here, we review the complex cause of ARDS, the molecular pathway of JAK/STAT involved in ARDS pathology, and the progress that has been made in strategies of targeting JAK/STAT to treat ARDS Specially, JAK/STAT signaling directly participates in the progression of ARDS or collude with other pathways to aggravate ARDS. We summarize JAK and STAT inhibitors with ARDS treatment benefits, including inhibitors in clinical trials and pre-clinical studies and natural products, and discuss the side effects of the current JAK inhibitors to reveal the future trends in designing of JAK inhibitors, which will help to develop effective treatment strategies for ARDS in the future.

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KEY WORDS Absorption of surplus fluid; ARDS; Cytokine release; Drug therapy; Epithelial function; JAK-STAT signaling; Smooth muscle proliferation

Running title: JAK-STAT signaling as an ARDS therapeutic target

Graphical Abstract

This review summarizes the role of JAK/STAT signaling in the development of ARDS, the progress of researches and future trends about JAK inhibitors, and that will help to develop effective treatment strategies for ARDS in the future.

1. Introduction

The acute respiratory distress syndrome (ARDS) is a serious respiratory failure caused by many factors including pneumonia, sepsis, aspiration of gastric contents or severe trauma which had a high mortality of up to 30-40% in most studies(Rubenfeld et al., 2005). With the outbreak of COVID-19, COVID-19 related ARDS induced higher fatality rates, and becomes a public health dilemma worldwide. Despite various studies in recent years, there is no effective pharmacotherapeutic agent emerging for the treatment of ARDS. Besides, decades of research still failed to find any effective therapies to reduce the mortality in established ARDS(Yadav, Thompson & Gajic, 2017).

Janus kinase (JAK) is vital transducer of many cytokines' intracellular signaling and involved in cell growth, survival, development, and differentiation of a variety of cells especially immune and hematopoietic cells(Ghoreschi, Laurence & O'Shea, 2009). There are 4 family members of Janus kinase, Jak1, Jak2, Jak3, and Tyk2. The signal transducer and activator of transcription family (STAT) is the most important transducer downstream of the JAKs. Type I and II cytokines binds to receptors, leading to the dimerization of the receptors, making the JAKs phosphate themselves, so leaving a docking site to the STATs. Then STATs are activated, translocated to the nucleus, and elicited specific transcriptional responses(Buchert, Burns & Ernst, 2016).

Cytokines related in the Janus kinase/signal transducer and activator of transcription pathway (JAK/STAT) signaling range from growth hormone, leptin, erythropoietin to ILs, and IFN. JAK/STAT signaling participates in proinflammatory machinery of the cellular immune response, heterochromatin stability. Since the first JAK2 inhibitor (ruxolitinib) approved for treating myelofibrosis by FDA at 2011, JAK inhibitors are making a brilliant figure in treating inflammation/autoimmune disease, metabolic homeostasis, tumor progression(Dodington, Desai & Woo, 2018).

As the outcome of JAK inhibitors in treating the COVID pneumonia recently(Guimaraes et al., 2021), JAK/STAT signaling becomes potential targets to cure ARDS, but it requires further validation of preclinical and clinical studies. Here, we review the pathogenesis of ARDS, JAK/STAT signaling in pulmonary physiology and pathology, JAK inhibitors of treating ARDS, and therapeutic agents based on JAK/STAT signaling for ARDS. We also discuss the future trends/strategies in JAK inhibitor design and usage in ARDS.

2. ARDS

The acute respiratory distress syndrome, also called acute lung injury, which is a common cause of respiratory failure in critically ill patients, is defined by the onset of noncardiogenic pulmonary oedema, hypoxemia and need for mechanical ventilation up to 1967(Ashbaugh, Bigelow, Petty & Levine, 1967). Over the last decades, the definition of ARDS becomes mature and forms the Berlin definition (Box 1) in 2012(Ranieri et al., 2012). Considering the 'sophisticated' measurements are not available in most developing areas, Riviello, E. D. et al. made up supplement to the Berlin definition, deleted the PEEP requirement and replaced the "PaO_2/FiO_2 <300 mmHg" to "SpO_2/FiO_2<315"(Riviello et al., 2016).

The normal lung is a space of carbon dioxide excretion and oxygen intake. This gas transfer function depends on the alveoli structure. The alveolar type I cells cover most of the alveoli have a function of gas transition. Between the alveolar type I cells is the alveolar type II cells which can exclude surfactant, the vital factor of reducing surface tension or enabling the alveoli to remain open and facilitating gas exchange. The alveolar type I and II cells form a tight barrier(Bhattacharya & Matthay, 2013). The alveolar type I and II cells have the capacity to absorb surplus fluid from the air space of alveoli by apical sodium channels and basolateral

Na^+/K^+-ATPase pumps(Matthay, 2014). In normal alveoli, there are macrophages, and they defense for the security of alveoli, which keep the normal function of alveoli.

Nevertheless, the alveolar type I and II cells are damaged in the ARDS, and there is much pulmonary dead space, leading to elevating of minute ventilation(Nuckton et al., 2002; Raurich et al., 2010). The mechanism of ARDS is complicated. Hallmarks of ARDS which has been widely accepted include the pulmonary epithelial cells injury (inflammatory injury and disruption of tight junctions), endothelial disruption and epithelial-endothelial barrier disfunction(Bachofen & Weibel, 1982). On the one hand, the bacterial or viral infection calls direct damage to pulmonary epithelial cells. On the other hand, in the indirect injury of pulmonary epithelial cells, the normal function of pulmonary capillary endothelial permanents is disturbed: the injured epithelial cells recruit neutrophils, macrophages from pulmonary parenchyma into the alveolar cavity, then the leukocytes release mass inflammatory mediators like ILs (IL-6, IL-1β), TNF, and angiopoietin. And they activate the endothelial cells, then permit platelets, erythrocytes and monocytes translate from capillary to alveolar cavity. The platelets and monocytes secrete protease, ROS, NETs. (Matthay, Ware & Zimmerman, 2012), which damage the alveolar epithelial cells once again. With the alveolar-capillary permeability increasing, the red blood cell accumulates to the alveolar and releasing hemoglobin that injured the VE-cadherin between the pulmonary endothelial(Bhattacharya & Matthay, 2013). All the above factors increased permeability to liquid and protein across the lung endothelium. Finally, the alveolar oedema became serious, and the function of alveoli, gas exchange, is destroyed.

There are many factors (pneumonia, toxic inhalation, pancreatitis, aspiration, trauma, sepsis, shock, alcohol, tobacco, high risk surgery, preexisting lung disease, radiation, chemotherapy, etc.)(Yadav, Thompson & Gajic, 2017) for the development of ARDS. After being exposed to one or more risk factors and failed to prevent the progress of ARDS in the very beginning, patients must rely on the ventilator to fulfill their need of oxygen. Even worse, that measures may give a second hit to the injured lung of patients(Wang et al., 2019). Eventually, it harms the brain, heart and has a lifelong term effect on the patients' life or even cause death.

It has passed nearly sixty years since the ARDS was first clearly defined. These years have witnessed the significant progress in the mechanism and pathophysiology of the ARDS. Lung-protective mechanical ventilation, fluid-restrictive resuscitation strategies, prone positioning, and the promotion of ventilator synchrony through the appropriate use of sedation and paralytic agents have all improved outcomes in ARDS, primarily by preventing further iatrogenic lung injury to an already injured lung(Yadav, Thompson & Gajic, 2017). Despite the management of some patients, the mortality of ARDS remains high. Besides, it failed to unfold any effective pharmacotherapy of ARDS. As the vital role of JAK/STAT in inflammation disease and the outcome of JAK inhibitors in treating the COVID pneumonia recently, JAK/STAT signaling becomes potential target to cure ARDS, and thereby it requires further validation of more clinical and preclinical studies.

3. The JAK-STAT signaling in ARDS

3.1 JAK-STAT signaling

3.1.1 JAK and STAT structure

JAK kinases' molecular weights are rigged 120-140kDa. They both contain seven conserved JH regions (JH1 ± JH7). They have four domains: FERM domain (a N-terminal four-point-one, ezrin, radixin, and meson; JH4˜7), SH2 domain (JH3˜4), a pseudo kinase domain (JH2), and a classical protein tyrosine kinase (PTK) domain (JH1)(Cai, Cai, Luo, Chen & Zhang, 2015). The JAK kinase mediated the signal transduction of almost 60 cytokines, hormones, and growth factors (GF)(O'Shea & Plenge, 2012).

The molecular weights of STAT proteins range from 79 to 113kDa, and they contain six domains: a N-terminal conserved domain, a DNA-binding domain, a SH3-like domain, a SH2 domains, and a C-terminal transcription domain. The N-terminal domain is vital for the STAT phosphorylation and the dimer-dimer interactions. The DNA binding domain usually locates between amino acids 400 and 500 and its function is

to form a complex of DNA with the STAT protein. The SH2 domain has been reported contribute to the protein-protein interactions of STATs and other proteins. The C-terminal transcription domain is required for the activation of STATs with highly conserved phosphorylated tyrosine (Y) and serine (S) residues(Gao, Liang, Shaikh, Zang, Xu & Zhang, 2018). Besides transduction of JAK signals, the STATs are also found directly transcriptional inducted by STAT target genes.

FIGURE 1 JAK and STAT structure.

3.1.2 Canonical JAK/STAT pathway

Cytokines like IFNs, colony stimulating factors, growth factors, and related molecules which have the similarity structure lack their own enzymatic activity. These cytokines' function relay seriously on series of JAK kinases in the intracellular cell signaling known as type I/II cytokines. Once they bind to their receptors on the cell membrane, the cytosolic domain of the receptors would initiate active JAK kinases, then creating docking sites for STAT. The JAK kinases include 4 memebers-JAK1, JAK2, JAK3 and TYK2(Waldmann & Chen, 2017). Each cytokine receptor intracellular domain connects with at least two JAK kinases. While the JAKs have an ability to deposit a phosphate on themselves or on other JAKs. After the JAK is phosphorated, they soon transfer their phosphates to STATs which are signal transducers and activators of transcription. Phosphorylated STATs become to dimers, move to the nucleus, then bind to the target gene promotors, thus activate the gene transcription(Banerjee, Biehl, Gadina, Hasni & Schwartz, 2017; Liongue, Sertori & Ward, 2016).

STATs contain an important class of molecules which transmit signals from type I/II cytokine receptors to nucleus. There are 7 STATs in mammals (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6). Different cytokines have the capacity to preferentially recruit different STATs. The STATs protein is very important to the immune system. At the very beginning STATs were linked with antiviral immunity, a key feature of STAT1 and 2(Shuai, Stark, Kerr & Darnell, 1993). STAT4 and STAT1 both can drive activated Th cells into a Th1 phenotype which is characterized by the secretion of IFN-?(Zhu, Yamane & Paul, 2010). STAT6 drives differentiation into an anti-helminth Th2 phenotype characterized by the secretion of IL-4, IL-5, and IL-13. STAT3, being activated by IL-6 and related cytokines, has diverse functions in many cells. In T cells, it drives differentiation into an antibacterial/antifungal Th17 phenotype characterized by the secretion of IL-17 and IL-22. Like STAT3, STAT5A and STAT5B are also activated by many cytokines including important hematopoietic factors like erythropoietin (EPO) and CSFs. In lymphocytes, STAT5 drives differentiation of innate lymphoid cells, promotes regulatory cell phenotype (Treg) and Foxp3 expression, and inhibits Th17 and follicular helper T cell differentiation(Gadina et al., 2018).

FIGURE 2 Activation of JAK kinases and its biological significance.

*Tyk2 seems to be important for signaling by gp130 and other cytokines but

the cell, cell-state, and species-specific requirements for gp130 cytokines are incompletely understood;

3.1.3 Non-Canonical JAK/STAT pathway

FIGURE 3 Non-canonical JAK-STAT signaling.

It's widely aberrated that the effects of STATs are mediated by direct transcriptional induction of STAT genes. However, in Drosophila and some mammal cells a non-canonical JAK-STAT pathway was identified, which directly controls the heterochromatin stability. That indicates the JAK affects the gene expression without directly STAT transcriptional control but by controlling cellular epigenetic STATs(Hixson, Cogswell, Brooks-Kayal & Russek, 2019; Li, 2008). Here comes a new mode of JAK signaling: JAK over-activation globally disrupts heterochromatin; that would enable expression of genes not necessarily under direct STAT transcriptional regulation(Betz & Darnell, 2006).

Different from the canonical mode of JAK-STAT (inactivated STATs distribution in the cytoplasm), in the non-canonical mode of JAK-STAT signaling, unphosphorylated STAT is localized on heterochromatin which is associated with HP1 in the nucleus. JAKs or other tyrosine kinases increase STAT phosphorylation,

that induces reducing in the amount of unphosphorylated STAT localized on heterochromatin, leads to HP1 displacement from heterochromatin and heterochromatin instability. On the one hand, dispersed phospho-STATs bind to cognitive sites in euchromatin to induce target-gene expression. On the other, genes originally localized in heterochromatin are now accessible to STAT or other transcription factors. Non-canonical JAK-STAT signaling regulates heterochromatin stability, resulting in altered histone H3 methylation and/or chromatin remodeling. The JAK/STAT over-activation disrupts heterochromatin [26]. Although, it has been demonstrated that perturbation of epigenetic gene regulation plays an important role in many human diseases like tumorigenesis. And there is still much that is unknown or poorly understood about the role of non-canonical JAK/STAT signaling in ARDS or other pulmonary diseases. There need more studies to reveal the JAK/STAT would cause how many kinds of disease in the human being.

3.1.4 Negative regulation of JAK-STAT pathway

In addition, there are three regulators and one activator identified in the JAK/STAT pathway: protein tyrosine phosphatases (PTPs), protein inhibitor of activated STAT (PIAS), suppressor of cytokine signaling (SOCS), and signal transducing adaptor molecule (STAM).

SHP-1, one of the PTPs, contains two SHP-2 domains, a catalytic PTP domain, a

divergent C-terminal region. SHP-2 domains bind to either the phosphorylated JAKs or other receptors to dephosphorylation these activated molecules(Bousquet, Susini & Melmed, 1999). Furthermore, other PTPs like PTP1B, CD45 and SHP2 are also reported roll in the JAK/STAT pathway(Irie-Sasaki et al., 2001; Xu & Qu, 2008; Yamada, Shiono, Joo & Yoshimura, 2003).

PIAS protein is another negatively regulator of the JAK/STAT pathway. It has five family members: PIAS1, PIAS3, PIASxα, PIASxβ, and PIASγ, each containing a putative Zn binding finger(Rawlings, Rosler & Harrison, 2004). It is an important transcriptional co-regulator of JAK-STAT. PIAS1binding to STAT1 inhibited its activity(Liao, Fu & Shuai, 2000; Liu et al., 1998). After IL-6 stimulation, PIAS3 was specific for the inhibition of STAT3-mediated gene expression(Borghouts, Tittmann, Delis, Kirchenbauer, Brill & Groner, 2010; Chung et al., 1997). PIAS was found also inhibit STAT1 associated gene expression not by affecting STAT1's DNA binding activity(Liu, Gross, Ten & Shuai, 2001; Tahk, Liu, Chernishof, Wong, Wu & Shuai, 2007). PIAS1 is also ubiquitinated by a ubiquitin E3 ligase, HECTD2. HECTD2 polymorphism, HECTD2(A19P), prevented HECTD2/PIAS1 nuclear interaction, thus prevented PIAS1 degradation and protected toward acute respiratory distress syndrome (ARDS)(Coon et al., 2015).

SOCS was found several years ago as a family protein of JAK inhibitors and protected against lipopolysaccharide-induced acute lung injury(Severgnini et al., 2005a). The SOCS contain eight members: CIS and SOCS1-SOCS7, each with a central SH2 domain and an ˜40 amino acid C-terminal region referred to as the SOCS box(Heinrich, Behrmann, Haan, Hermanns, Muller-Newen & Schaper, 2003). SOCS proteins are thought to bind to STAT5 and inhibit the activity of the receptor or JAK. CIS complete with STAT5 so modulate JAK2/STAT5 pathway(Cooney, 2002; Matsumoto et al., 1997; Yoshimura, 1998a; Yoshimura, 1998b). SOCS1 and SOCS3 are related in inhibition of IL-6-type cytokine signaling by inhibiting phosphorylation of gp130,STAT,JAK(Endo et al., 1997): SOCS1 bind to the activation loop of JAKs by its SH2 domain(Sasaki et al., 1999); nevertheless, SOCS3 may bind to the phosphoserine motif 759 of JAK2 and also bind to activation loop of JAK2 via its SH2 domain(Nicholson et al., 2000; Schmitz, Weissenbach, Haan, Heinrich & Schaper, 2000). And SOCS1 probably block JAK activity more efficient than SOCS3(Heinrich, Behrmann, Haan, Hermanns, Muller-Newen & Schaper, 2003).

The STAM proteins associated with JAKs are phosphorylated in response to cytokines, and serve to increase signaling(Pandey et al., 2000). So far, four members of the STAM family have been identified in human (STAM1, STAM2A, STAM2B, and EAST). All STAMs have a 140 amino acid VHS (present in Vps-27, Hrs, and STAM) domain in their N terminus, a central SH3 domain, and an ITAM motif (except STAM2B) in their C terminus.

3.2 JAK/STAT expression pattern in lung

The expression of JAK/STAT in lung is mostly studied in the lung tumor (non-small-cell lung carcinoma), interstitial lung disease (ILD), asthma and acute lung injury. Different kinds of pulmonary diseases vary in the expression and distribution of JAK/STAT. Among the members of JAK and STAT protein families, JAK1, JAK2, and STAT1, STAT3 are most studied. Especially, JAK1/3 signaling pathways are considered key initiators of TH2 differentiation and lung allergic responses(Ashino et al., 2014). It is generally considered the JAK/STAT signaling is a transducer of cytokines, and many researches of JAK/STAT are about their role in immune cells, however, there is rarely study about their mechanism in pulmonary parenchyma cells.

JAK1/STAT3 signaling participated in the inflammation lung diseases. The activation of JAK1/STAT3 is related to many kinds of inflammation lung injury and is the cause or consequence of the imbalance in lung microenvironment. JAK1-associated PI3K signaling regulates gene induction of inflammation cytokines[53]. In addition, IL-17A is revealed of participating in the acute lung injury process, it upregulated p-JAK1/2, p-STAT1/3, stimulated inflammation gene induction in human airway epithelial cells by JAK1-associated PI3K signaling(Shaikh, Bhat & Bhandary, 2020). In the respiratory inflammatory response process, JAK1 and STAT3 stimulated the -500 to +41 promoter activity of the surfactant protein B (SP-B) gene in respiratory epithelial cells, influence on surfactant protein homeostasis(Yan, Naltner, Martin, Naltner, Fangman & Gurel, 2002).

Numerous studies show JAK1 is activated by many factors in the process of "one hit lung injury" (induced by virus infection, hyperoxia, tobacco, etc.) and "second hit lung injury" (such as ventilator induced lung injury), and inhibition of JAK1 is postulated to be able to reduce lung injury. In BEAS-2B cell, the viral infection process elevated JAK1 expression(Zhou, Wang, Li, Wang & Hou, 2021). In fetal type II epithelial cells, the mechanical stretch exposure activated IL-6-STAT3-SOCS3 signaling pathway decreased IL-10 signaling pathway, activated JAK1, TYK2 and finally induced the injury of mechanical(Hokenson, Wang, Hawwa, Huang, Sharma & Sanchez-Esteban, 2013). There are also studies about hyperoxia which found hyperoxia exposure activated IL-10 signaling and JAK1, TYK2(Lee & Lee, 2015). In primary human small airway epithelial cells, IL-13-induced metaplasia (expression of Muc5AC, Muc5B, and SPDEF) and it is due to the phosphorylation of JAK-1, ERK1/2, and STAT-6. The aldose reductase could prevent metaplasia of airway epithelial cells by inhibition of JAK/STAT(Yadav, Leopoldo, Ramana, Istvan, Srivastava & Melanie, 2010). In tobacco injured lung injury, inhibition of JAK1 and STAT3 decreased the SOCS-3 expression, and restored tobacco injured airway epithelial cells(Nasreen, Gonzalves, Peruvemba & Mohammed, 2014). In cultured human bronchial smooth muscle cells STAT6 phosphorylation/activation induced by IL-13 was mediated by activation of JAK1(Yoshihiko, Kumiko & Miwa, 2012).

Recent researches reveal that JAK3 abnormally activated in many lung diseases. JAK3 kinase is first cloned from rat tissues including spleen, lung, kidney, and intestine(Takahashi & Shirasaw, 1994). Subsequently, JAK3 is verified playing a vital role in the proliferation of hematopoietic cells especially T lymphocytes(Cetkovic-Cvrlje & Uckun, 2004) but then it was also found that JAK3 was important in myeloid cells and epithelial cell barrier function. Inflammation microenvironment abnormally activated JAK3 kinase, subsequently injured the epithelial barrier function, in return aggravated inflammation injury to epithelial cells. Cancer gene profile of lung cancer patients showed that there were JAK2 and JAK3 active mutations in the condition of lung diseases(Li et al., 2017). JAK3 inhibitors decreased MUC4 mRNA level of pseudo stratified columnar epithelium, alleviated epithelial cell injury, and regulated its hyperplasia(Damera, Xia & Sach De V, 2006). JAK3 transduce is also critical for eosinophil recruitment in airway inflammation(Li et al., 1999). The activating of JAK3/STAT5 pathway promotes airway smooth muscle cell inflammation(Zhu, Huang, Zhu & Cai). In the monocyte/macrophage, JAK3 signaling enhances IL-10 production leading to down-regulation of IL-1 beta-converting enzyme (ICE) activation and suppression of IL-1 beta processing and releasing. Hence, targeting JAK3 is potentially therapeutic to pulmonary inflammation and other lung diseases (idiopathic pulmonary fibrosis, COPD)(Li, Wang, Wang & Zhang, 2017; Yz et al.; Zhou, Zhuo & Cai, 2018).

Existing evidence suggests that JAK2 plays a negative role in pulmonary inflammation. Inhibition of JAK2, JAK1, STAT1, STAT3 and TYK2 ameliorate the acute lung injury or inflammation pathology(Li, Cao,

Xiang, Hong & Huang, 2020; Liu, Dong, Bo, Li & Li, 2015; Song et al., 2015). There are also study shows that increasing of the tyrosine phosphorylation of TYK2, JAK3 induced STAT3 and STAT5 tyrosine phosphorylation, then stimulated proliferation of pulmonary epithelial cells(Liu & Kern, 2002).

Moreover, the JAK1/JAK2/STAT1/STAT3/STAT6 and TYK2 are also reported to have a closely connection with other pulmonary diseases like intestinal pulmonary fibrosis (IPF), pulmonary sarcoidosis(Montero, Milara, Roger & Cortijo, 2021). And up-regulation of their phosphorylated form is often related to disease progression and poor prognosis. These findings highlight that JAK-STAT signaling is closely linked with pulmonary physiology and pathophysiology.

3.3 JAK-STAT signaling in ARDS

3.3.1 JAK-STAT related cytokine release and immune response

IL-6 is a vital factor in ARDS which relays on JAK/STAT transfer the signaling. IL-6 related JAK-STAT activation has a negative impact on the disease progression of ARDS (caused by tobacco, ventilator, etc.). In the VILI (ventilator-induced lung injury), intratracheal IL-6 administration in C57BL/6J mice increased protein content and cell count in bronchoalveolar lavage fluid, which was associated with activation of JAK signal transducers, activators of transcription, p38 MAP kinase, and NF-ϰB signaling(Birukova, Tian, Meliton, Leff, Wu & Birukov, 2012). Moreover, IL-6 can enlarge the endothelial cell (EC) permeability in the situation of pathologically relevant cyclic stretch (CS) magnitudes, increase ICAM-1 expression of pulmonary EC and neutrophil adhesion. However, Rho kinase inhibitor Y-27632 suppressed the synergistic effect. That is evidence of Rho taking part in the endothelial integrity(Gudipaty & Rosenblatt, 2017). Other study also shows that influenza A virus infection induced muscle wasting via IL-6 regulation of the E3 ubiquitin ligase atrogin-1(Radigan et al., 2019). Glucocorticoids like betamethasone (BTM) and dexamethasone (DXM), potentiate IL-6-induced SP-B expression in H441 cells by enhancing the JAK-STAT signaling pathway, so make a negative impact on ARDS(Ladenburger et al., 2010a).

In the mouse model of severe influenza A pneumonia, IL-6 promoted muscle degradation via the E3 Ubiquitin Ligase atrogin-1, STAT3, FOXO3a(Shaikh, Bhat & Bhandary, 2020). There is also study shows that glucocorticoids potentiate IL-6-induced SP-B expression in H441 cells by enhancing the JAK-STAT signaling pathway and that phenomenon is reversed by JAK1 inhibitor(Ladenburger et al., 2010b). Not only IL-6, there are many other cytokines, like IL-17A participated in the in vivo mice model of ALI, may related to ARDS(Shaikh, Bhat & Bhandary, 2020).

As to STAT (1/3) is activated in ARDS, targeting STAT3 may be therapeutical to ALI and ARDS patients(Severgnini et al., 2004). In LPS-induced ALI mouse model STAT3 was activated in CD45+CD11b+ cells from BALF and in LPS treated macrophages in vitro. STAT3 inhibitor LLL12 decreased IL-1β, IL-6, TNF-α, iNOS, CCL2, and MHC class II in macrophages and inflammatory cells from BALF and serum determined by ELISA. Hyperactivation of STAT3 in LysMCre-SOCS3fl/fl mice accelerated the severity of inflammation in the ALI model(Zhao et al., 2016). Myeloid, Ly6C (+) macrophage, lack of SOCS3 resulted in more expression of STAT3 and increased LPS-induced murine acute lung injury(Jiang, Chen, Li, Zhou & Zhu, 2017).

In recent research about alveolar macrophage transcriptional program in patients, cell-specific AM (alveolar macrophage) proinflammatory and M1-like(IL-6/JAK/STAT5 activation) at the time of ARDS onset were associated with better clinical outcomes(Morrell et al., 2019). Decreasing of p-JAK1, p-STAT1, p-STAT3, and PKM2-mediated glycolytic pathways could reverse lipopolysaccharide-induced inflammatory responses of macrophages(Ying, Li, Yu & Yu, 2021). Not only macrophages, there was also study about the mesenchymal stem cells (MSCs). They affected ARDS in newborn swine via JAK-STAT signaling pathway. MSCs increased interleukins (IL-2, IL-6, IL-8), and tumor necrosis factor-α (TNF-α) expression levels and decreased IL-10 and IL-13.

3.3.2 JAK-STAT in epithelial function/ smooth muscle proliferation and surplus fluid absorption

JAK is vital for the epithelial functions. JAK3 was found interacts with cytoskeletal proteins so play an essential role in cytoskeletal remodeling and epithelial wound repair(Kumar, Mishra, Narang & Waters, 2007). In mucosal homeostasis, JAK3 interacted with adapter protein p52ShcA and regulated the expression of differentiation markers, formation of mucus in mice, and facilitated barrier functions through its interactions and adherent junction (AJ) localization. In DSS mouse model, knockdown of JAK3 decreased TEER and AJ localizations of β-catenin induced increasing of severity in DSS-induced colitis. JAK3 activation led to β-catenin phosphorylation at Tyr-654, which promoted β-catenin interaction with E-cadherin, thereby facilitated AJ formation and enhanced the IEC barrier functions. The expression of differentiation markers of human intestinal epithelial cells (IEC) depended on the nuclear translocation of phosphorylated form of JAK3(Mishra, Verma, Alpini, Meng & Kumar, 2013). In the region of SHC, the CH1 and PID domains were responsible for binding to JAK3. In situation of IL-2 stimulated of epithelial cells, JAK3 was auto-phosphorylated. However, SHC recruited tyrosine phosphatases SHP2 and PTP1B to JAK3, thereby dephosphorylated JAK3(Mishra & Kumar, 2014).

Additionally, Surfactant protein C, a key component of pulmonary surfactant, which is a specific marker of type II alveolar epithelial cells, is convinced has a connection with JAK/STAT. Misfolded proSP-C caused subsequently type II alveolar cell injury and inflammation(Hamvas et al., 2004). The SPC-TK/SPC-KO (surfactant protein C-thymidine kinase/surfactant protein C knockout) mice showed enhancing Janus kinase (JAK)/STAT activation which is associated with increased inflammation and delayed repair(Alsulaimani, 2018). Clinical trials about ARDS patients' treatment with exogenous recombinant surfactant protein C(rSP-C)-based surfactant resulted in improvement in blood oxygenation and suggested a potential benefit(Spragg et al., 2004).

JAK3 plays a critical role in smooth muscle proliferation and injury-induced neointima formation. Despite JAK3 has a low level of expression in normal vascular SMCs, the expression and activity of JAK3 are dramatically induced by PDGF-BB in vitro and by balloon injury in vivo(Wang, Cui, Chuang & Chen, 2017a). Thus, JAK3 is potential a therapeutic target to preventing neointimal hyperplasia in proliferative vascular diseases. Moreover, JAK2 is reported regulating angiotensin II induced smooth muscle proliferation and vascular remodeling(Wang, Cui, Chuang & Chen, 2017b). In vitro ALI model, LPS-induced upregulation of the PI3K/AKT and JAK/STAT signaling pathways in human lung fibroblast, was further inhibited by KLF4 knockdown(Li, Zhang & Yang, 2019). Muscle dysfunction, associated with JAK/STAT activation, is related to the low mobility of ARDS(Files, Sanchez & Morris, 2015).

JAK2 and JAK3 are both potent regulators of Na+/K+ ATPase(Bhavsar et al., 2014; Hosseinzadeh et al., 2015). That reveals JAK/STAT may participate in the absorption of surplus fluid during ARDS process by the Na^+/K^+-ATPase. In energy depletion model of DCs and Xenopus laevis oocytes which treated with 2,4-dinitro-phenol, JAK3 was phosphorylated (and therefore activated), and JAK3 downregulated the Na+/K+-ATPase. Pharmacological inhibition of JAK3 significantly increased Na^+/K^+-ATPase(Hosseinzadehet al., 2015). Recent studies found that JAK3 directly affected the transport proteins in partial, including various ion channels, a number of cellular carriers and the Na^+/K^+pump including the high-affinity Na^+ coupled glucose transporter SGLT1, the excitatory amino acid transporters EAAT1, EAAT2, EAAT3 and EAAT4, the peptide transporters PepT1 and PepT2, CreaT1 and the Na^+/K^+-ATPase(Sopjani, Thaci, Krasniqi, Selmonaj, Rinnerthaler & Dermaku-Sopjani, 2017). There need additional experiments to elucidate the mechanisms and prerequisites of up- or down-regulation of Na^+/K^+-ATPase by JAK3 or JAK2.

Moreover, JAKs also phosphate SHP-2 or PI3K, thus play an important part in other signal transduction pathways such as Ras/Raf/MAPK/ERK pathway and PI3K-AKT pathway(Saxena et al., 2007; Wit & de Luca, 2016). Besides, ROS is revealed participated in the activation of JAK-STAT signaling and in the pathogenesis of ARDS. In fibroblasts and A-431 carcinoma cells, treatment of H_2O_2 can activated STAT1, STAT3 and STAT kinases JAK2 and TYK2 within 5min. And PDGF uses ROS as a second messenger to regulate STAT activation(Simon, Rai, Fanburg & Cochran, 1998).

4. JAK inhibitors in ARDS

4.1 JAK inhibitors in clinical trials approved by FDA

Traced back to 2000th, the tyrosine kinase inhibitor imatinib successed in the treatment of chronic myelogenous leukaemia. Immediately followed by imatinib, dozens of kinase inhibitors were approved for the treatment of various cancers. In 2011th, the first JAKinib ruxolitinib targeting JAK2 was designed for neoplastic gain FDA approval . Mutation of V617F in JAK2 results in constitutive activation downstream of erythropoietin (EPO), GM-CSF and thrombopoietin (TPO) receptors. And it is associated strongly with myeloproliferative neoplasms including myelofibrosis, polycythaemia vera (PCV) and essential thrombocythaemia(Lundberg et al., 2014). On the one hand, as to JAK-STAT pathway is constitutively activated in many kind of cancer, recently JAKnibs are approved in many clinical trials treating haematological and solid tumours(Johnson, O'Keefe & Grandis, 2018). On the other hand, in the recent years, JAKnib find its usage in treating inflammatory and immune disease, such as rheumatoid arthritis, inflammatory bowel disease(IBD) and psoriasis. Futher more, as to cardiovascular disease (CVD) is increasingly being seen as an inflammatory process, JAKnib is found potential in treating atherosclerosis(Tang et al., 2020; Yang et al., 2020). There are also preliminary data showed the potentian of tofatinib (pan-JAK inhibitor) in treating diabetic nephropathy(Tuttle et al., 2018). Recently, JAK inhibitors are also point out to be potential theraputic candidates of treating asthma(Sada, Watanabe, Nakamoto, Inui & Takizawa, 2020; Yu, Shi, Shu, Ding & Lou, 2021), COPD(Beaulieu, Attwe, Breau, Lipskaia & Adnot, 2021), ARDS and COVID-19 cytokine release syndrome(Luo, Li, Jiang, Chen, Wang & Ye, 2020).

It has passed nearly 20 years from the first generation pan-JAK inhibitors approved in treating myelofibrosis or rheumatoid arthritis. There are more selective JAK inhibitors designed to adjust different medical demand and they overcome the side effects of suppressing so many cytokines indiscriminately(Kim et al., 2020)·(Zhu et al., 2020).

FIGURE 4 Chemical structure and attributes of various JAK inhibitors. The first-generation Janus kinase (JAK) inhibitors ruxolitinib, tofacitinib and baricitinib block multiple JAKs. The newer pan-JAKinib peficitinib has a median inhibitory concentration (IC50) of 3.9, 5.0, 0.71 and 4.8 nmol/L for JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) enzymatic activity, respectively. A variety of next-generation JAK inhibitors are emerging. Several block JAKs and other kinases (R333, cerdulatinib and pacritinib), whereas many are selective for one JAK isoform. Filgotinib, upadacitinib and solcitinib block JAK1; Decernotinib, PF-06651600, tubulosine, JANEX-1 (WHI-P131) block JAK3; and BMS986165, NDI-021232, NDI-031407, PF-06700841 and SAR-20347 all block TYK2. Chemical structures are shown.

4.2 JAK inhibitors in treating ARDS

Inhibition of JAK kinase may suppress ARDS and pneumonia for JAKs enrolled in the function and concentrations of pro-inflammatory cytokines, and JAKs play a vital role in pulmonary physiopathology especially epithelial cell barrier function. The potential therapeutic effects of JAK inhibitors in ARDS become revealed as the outbreak of the COVID related pneumonia and become a new crucial strategy for dealing with other types of ARDS.

4.2.1 JAK inhibitors for COVID-19 induced ARDS

JAK inhibitors could be considered an option for treating COVID-19-related ARDS or pneumonia patients for two reasons. On the one hand, JAKs are involved in JAK/STAT signaling which is associated with the receptors of a large variety of cytokines(Convertino et al., 2020), as the major patients of ARDS showed a phenomenon of "cytokine storm", related to the severity of disease, that high circulating levels of interleukins (IL)-2, IL-6, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), 10kDa interferon-gamma-induced protein (IP-10), monocyte chemo-attractant protein-1 (MCP-1), macrophage inflammatory protein 1α (MIP-1α), and tumor necrosis factor (TNF) (Guo et al., 2020; McGonagle, Sharif, O'Regan & Bridgewood, 2020). Especially, in ARDS patients, a strong depletion of peripheral blood T cells, along with a decreased recruitment of lymphocytes and neutralizing antibodies and an increased production of cytokines, was detected in the lungs(Qin et al., 2020). On the other, the selective JAK1/2 inhibitor, baricitinib, is shown to hinder the endocytosis and assembly of the SARS-CoV-2 to the host cell by inhibiting AP2-associated protein kinase 1

(AAK1) (Aslan & Akova, 2021; Saber-Ayad et al., 2021). So far, there are over dozens of clinical trials for JAK inhibitors (including ruxolitinib, baricitinib, tofacitinib, nezulcitinib (TD-0903)) and their combined application with other anti-viral drugs like remdesivir treating the COVID related pneumonia around world-wide(Giudice et al., 2020). And therapeutic strategy ranges from oral administration to inhalation(Aslan & Akova, 2021; Saber-Ayadet al., 2021; Singh et al., 2021).

Recently, a meta-analysis about JAK-inhibitors for coronavirus disease-2019 enrolled 2367 subjects found that the usage of JAK-inhibitors decreased the invasive mechanical ventilation (RR = 0.63; [95% Confidence Interval (CI), 0.47, 0.84]; P = 0.002) and had borderline impact on rates of intensive care unit (ICU) admission (RR = 0.24 [0.06, 1.02]; P = 0.05) and acute respiratory distress syndrome. did not decrease interval of hospitalization. The risk of death was decreased, most convincingly for baricitinib(Chen, Wang, Li, Yuan, Gale & Liang, 2021; Patoulias, Doumas, Papadopoulos & Karagiannis, 2021). JAK-inhibitors play a potential role in reducing the risk of death in persons with COVID-19. While, the underling mechanism of therapeutic benefits is not clearly studied.

In the in vivo mouse model of SARS-CoV-2 spike protein induced ARDS cytokine storm, the JAK1/2 inhibitor, baricitinib and febratinib have the different outcomes, JAK1/2 inhibitor baricitinib significantly reduced the production of IL-6, but the JAK2 inhibitor febratinib did not and baricitinib led to obvious decrease in neutrophilic inflammation and interstitial edema(Gu et al., 2020).

While there are also other natural products, which are convinced inhibit the JAK/STAT, are potential candidates of treating COVID or COVID related ARDS. The flavonolignan silibinin is a direct inhibitor of STAT3, regulate inflammatory cytokine signaling and immune response, thus may play a combination role of IL-6-targeted monoclonal antibodies and pan-JAK1/2 inhibitors in treating COVID(Bosch-Barrera, Martin-Castillo, Buxo, Brunet, Encinar & Menendez, 2020).

4.2.2 JAK inhibitors in the in vivo experimental ARDS mouse model

Suppressing STAT3 activity also have protective effect in LPS-induced acute lung injury(Zhaoet al., 2016) In a novel sterile injury model of SPC-TK/SPC-KO (surfactant protein C-thymidine kinase/surfactant protein C knockout) mice, AZD1480, a JAK1/2 inhibitor decreased hyperactivation of pSTAT3 and inflammation, reveals the surfactant protein C regulating JAK/STAT activation in lung repair of ALI(Jin et al., 2018).

In the cecal ligation puncture (CLP) procedure rat model of ALI, the methotrexate ameliorates systemic inflammation(Bringué et al., 2021). Natural immunosuppressant compounds, derived from plant sources such as release of pro-inflammatory cytokines and chemokines. This inhibitory effect is mediated by altering signal pathways like NF-ϰB, JAK/STAT(Peter, Sandeep, Rao & Kalpana, 2020),. Natural astaxanthin alleviated the risk of cytokine storm (IL-1β, IL-6, IL-8, TNF-α) in COVID-19 via JAK/STAT signaling(Talukdar, Bhadra, Dattaroy, Nagle & Dasgupta, 2020).

In the mouse model of ALI, the Src, JAK2, STAT3 are activated. The tyrosine inhibitor (PP2, SU6656, Tyrphostin A1) significant attenuated LPS induced ALI determined by histologic and capillary permeability assays, blocked LPS-dependent cytokine and chemokine production in the lung and serum(Severgnini et al., 2005b). Oxidative stress imbalance and apoptosis are the main characters of ventilator-induced lung injury (VILI), intermedin has anti-oxidative stress and anti-apoptotic effects via JAK2/STAT3 signaling, thus may prevent and treat the VILI(Fan, He, Yang & Wang, 2021).

4.3 Side effects

As the application of JAK inhibitor in ARDS barely started in the resent years, the side effects are almost revealed in the usage of treating other immune related disease such as IBD and RA. Pan-JAK inhibitors block a broad of cytokines, ILs, IFNs, hormones and growth factors. Widely inhibition of the upon factors contribute to many adverse events ranges, such as infections, hematological or cardiovascular affects, malignancies, and gastrointestinal perforations.

Since blockage of many cytokines in host defense, infections become a common adverse event of JAK in-

hibitors. One common infection in tofacitinib and baricitinib treated patients is reactivation of varicella zoster virus. The exact mechanism is unclear: inhibit IFN production may cause impairment of anti-viral immunity(Favalli, Biggioggero, Maioli & Caporali, 2020). In addition, inhibition of JAK1 and JAK3 reduced the NK, innate lymphoid and CD8+T cells in numbers and functionally. The possibility of diverticulitis is another disadvantage of JAK inhibitors(Jamilloux, El, Vuitton, Gerfaud-Valentin, Kerever & Seve, 2019).

Moreover, JAKs especially JAK2 lead to hematological effects (decreasing of lymphocytes, NK cells, neutrophils, platelets, and anemia)(Wollenhaupt et al., 2019). The decreasing of hemoglobin probably related to inhibition of EPO or other JAK2 related cytokines. There are also study shows that JAK inhibitors increase the high- and low-density lipoproteins and thromboembolic evens(Rao et al., 2015). The underling mechanism or whether it is related to cardiovascular effects is not clearly studied until now. Additionally, due to the blockage of IL-6 signaling, pan-JAK inhibitor is reported increasing the property of gastrointestinal perforation.

4.4 Next generation JAK inhibitors

Unlike JAK1 and JAK2 inhibition impacts numerous cytokines and have widely effects on their functions, JAK3 and TYK2 are related to a smaller kind of cytokines. More selective JAK3 or TYK2 inhibition may be a strategy of the side effects beyond pan-JAK inhibitors. Even if there may cost an extent of efficacy. Up to now, two JAK3 inhibitors, decernotinib and PF-06651600, are in clinical trials study (treating RA, alopecia areata, CD, and UC). While theoretically blocking JAK3 should only inhibits γC related cytokinesis. However, decernotinib also shows affecting CYP3A4 thus influence metabolism of statins and other drugs(Zetterberg et al., 2016). Another strategy to decrease the affection of JAK2 dependent cytokines is JAK1 selective inhibitor. Five JAK1 selective inhibitors, filgotinib, upadacitinib (ABT-494), itacitinib, PF-04965842, GSK2586184, are in the stage of clinical trials. Additionally, restricted to targeting IL-12, IL-23, type I, and type III IFNs, TYK2(BMS-986165, PF-06700841) selective inhibitors have the superiority of utility in IBD and SLE with more partially side effects. Besides the selective JAK inhibitors, considering the complicated mechanism of many diseases, combined inhibitors such as cerdulatinib (targets SYK/JAK)(Coffey et al., 2014), pacritinib(targets JAK2/FLT3)(Hatzimichael, Tsolas & Briasoulis, 2014), with two or more target kinases may broader the usage in treating disease.

Furthermore, targeting JAK upstream suppressor kinases such as SOCS or downstream STATs including oligonucleotide-based STAT inhibitors, STAT-targeting small molecules, inhibitory peptides, and siRNAs(Miklossy, Hilliard & Turkson, 2013; Sen & Grandis, 2012) represent a new territory and their effects in ARDS remain to be convinced.

5. Conclusions and prospects

JAK/STAT signaling is getting more recognition in its vital role in cell growth, survival, development, and differentiation of immune and epithelial cells. And multiple JAK inhibitors have been approved for treating inflammation disease. Recent studies about JAK inhibitors for treating COVID-related ARDS, present the possibility of JAK/STAT in pharmacotherapeutic ARDS. This review summarized the corresponds of JAK/STAT and ARDS, expounded the JAK inhibitor's research status in treating ARDS and discussed the future trends in design and strategy of JAK inhibitors. The mechanism of ARDS is complex. Although it has passed decades from the ARDS was first defined, there is sincerely any progress in the therapeutic pharmacy of ARDS. Based on the current findings, JAK/STAT is probably to be an outbreak in this field.

JAK/STAT is critical in the signal transduction of many important inflammation cytokines which play a vital role in ARDS "cytokine storm". JAK/STAT is also participated in the epithelial homeostasis and pulmonary physiopathology. As JAK inhibitors is starting its clinical trials in ARDS, there are also many items to be considered. To continue to expand JAK inhibitors usage, there is a need for further development and refinement of efficient selective JAK inhibitors. In different type and cause of ARDS, JAK inhibitors may have different pharmacological effects. We also need more studies to find out the outcome of JAK inhibitors in different stage of ARDS and how many diagnose indicators are ameliorated in the progress.

Additionally, the canonical and non-canonical JAK/STAT signaling and their role in the ARDS is looking forward to be fully revealed to discover novel targets of ARDS. It also prompts investigation of understudying the JAK/STAT role in pulmonary pathophysiology and promote the therapy of other pulmonary diseases.

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TABLE 1 The 2021 Berlin definition of ARDS.

2012 Berlin definition

Timing	respiratory failure within 1 week of a known insult or new and/or worsening respiratory symptoms
Origin	respiratory failure not fully explained by cardiac function or volume overload (need objective criterion such a
Imaging	bilateral opacities on chest radiograph or CT not fully explained by effusion, collapse, or nodules
Oxygenation	acute onset of hypoxemia defined as PaO2/FiO2 <300 mmHg on at least PEEP 5cmH_2O – PaO_2/FiO_2 of 201'-300 mmHg is mild ARDS – PaO_2/FiO_2 of 101-200 mmHg is moderate ARDS – PaO_2/

TABLE 2 Clinical trials using JAK inhibitors for various clinical indications.

Selectivity	Preparation	Status	Approval	NCT Number
JAK1i	Filgotinib	II	Noninfectious Uveitis	NCT03207815
		III	Ankylosing Spondylitis	NCT04483700

Selectivity	Preparation	Status	Approval	NCT Number
		III	Psoriatic Arthritis	NCT04115839
		II	Lupus Membranous Nephropathy	NCT03285711
		II	Cutaneous Lupus Erythematosus	NCT03134222
		I	Renal Impairment	NCT02084199
		II	Sjogren's Syndrome	NCT03100942
		II	Inflammatory Bowel Disease	NCT03201445
	PF04965842	I, III	Dermatitis, Atopic	NCT03634345
		II	Plaque Psoriasis	NCT02201524
	Oclacitinib	Approved	Atopic dermatitis	
JAK2i	GSK2586184	I	Colitis, Ulcerative	NCT02000453
		I	Systemic Lupus Erythematosus	NCT01953835
		I	Psoriasis	NCT01782664
		I, II	Systemic Lupus Erythematosus	NCT01687309; NCT01777256
	Pacritinib	I	Myelofibrosis	NCT02765724
		II	Prostates Cancer	NCT04635059
		II	Acute Myeloid Leukemia (AML)	NCT02532010
		I	Lymphoma, T-Cell, Cutaneous Lymphoma, T-Cell, Peripheral Chronic Lymphocytic Leukemia	NCT03601819
		II	Colorectal Cancer	NCT02277093
		II	Leukemia	NCT02469415
		I, II	GVHD	NCT02891603
		I	Non-Small Cell Lung Cancer	NCT02342353
Selectivity	Preparation	Status	Approval	NCT Number
JAK2i	Pacritinib	I	Non-Small Cell Lung Cancer	NCT02342353
		I, II	Breast Cancer	NCT04520269
		III	COVID19	NCT04404361
JAK3i	PF-06651600	II, III	Alopecia Areata	NCT03732807; NCT02974868; NCT04006457; NCT04517864
		II	Rheumatoid Arthritis	NCT02969044; NCT04413617
		II	Ulcerative Colitis	NCT02958865
		II	Crohn's Disease	NCT03395184

Selectivity	Preparation	Status	Approval	NCT Number
TYK2i	BMS986165	II, III	Psoriasis; Plaque Psoriasis	NCT05065762; NCT02931838; NCT03611751; NCT04167462; NCT03924427; NCT04036435; NCT04772079
		III	Psoriatic Arthritis	NCT04908189; NCT04908202
		II	Ulcerative Colitis; Colitis, Ulcerative; Granulomatous; Colitis Crohn's Disease; Crohn's Enteritis; Granulomatous Enteritis	NCT03934216; NCT04613518; NCT03599622; NCT04877990
		II	Systemic Lupus Erythematosus; Lupus Erythematosus, Discoid Lupus Erythematosus; Subacute Cutaneous	NCT03252587; NCT04857034
	PF-06826647	II	Psoriasis	NCT03895372
		II	Ulcerative Colitis	NCT04209556
		II	Acne Inversa	NCT04092452
	PF-06835375	II	Primary Immune Thrombocytopenia	NCT05070845

Selectivity	Preparation	Status	Approval	NCT Number
JAK1/JAK2i	Baricitinib	Approved	Rheumatoid arthritis	
	CTP-543	II, III	Alopecia Areata	NCT05041803; NCT03898479; NCT04784533; NCT03941548; NCT03811912; NCT04797650; NCT04518995
	PF06700841	II	Systemic Lupus Erythematosus	NCT03845517;
		II	Atopic Dermatitis	NCT03903822
		II	Psoriatic Arthritis; Alopecia Areata	NCT03963401
		II	Chronic Plaque; Psoriasis; Psoriasis	NCT02969018; NCT03850483

Selectivity	**Preparation**	**Status**	**Approval**	**NCT Number**
		II	Crohn's Disease; Ulcerative Colitis	NCT03395184; NCT02958865
		II	Acne Inverse	NCT04092452
		II	Alopecia Areata; Cicatricial Alopecia	NCT02974868; NCT05076006
		II	Active Non-segmental Vitiligo	NCT03715829
	Ruxolitinib	Approved	Polycythemia vera, intermediate-high risk myelofibrosis	
	Upadacitinib	Approved	Rheumatoid Arthritis	
JAK1/JAK3i	ATI-501	II	Alopecia; Areata Alopecia; Universalis Alopecia; Totalis;	NCT03759340; NCT03594227
	ATI-502	II	Alopecia Areata; Alopecia; Universalis Alopecia; Totalis; Atopic Dermatitis	NCT03759340; NCT03585296
	Tofacitinib	approved	Rheumatoid Arthritis, Psoriatic Arthritis, Ulcerative Colitis	

Selectivity	Preparation	Status	Approval	NCT Number
JAK1/TYK2i	PF06700841	II	Systemic Lupus Erythematosus	NCT03845517
		II	Atopic Dermatitis	NCT03903822
		II	Psoriatic Arthritis; Alopecia Areata	NCT03963401; NCT029
		II	Chronic Plaque Psoriasis; Psoriasis; Cicatricial Alopecia	NCT02969018; NCT038
		II	Crohn's Disease; Ulcerative Colitis	NCT03395184; NCT029
		II	Active Non-segmental Vitiligo	NCT03715829
		II	Acne Inversa	NCT04092452