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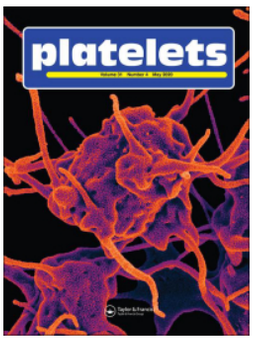

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REVIEW

Recent advances in understanding spleen tyrosine kinase (SYK) in human biology and disease, with a focus on fostamatinib

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Abstract

Spleen tyrosine kinase (SYK) is an important regulatory molecule of signal transduction pathways involved in the pathogenesis of autoimmune diseases such as immune thrombocytopenia (ITP), and the SYK-signaling pathway has emerged as a potential target for the treatment of numerous diseases. The aim of this narrative review is to summarize the biological properties of SYK and its involvement in disease pathways, provide an update on SYK inhibitors in the treatment of ITP, and consider other potential applications. Fostamatinib, the only licensed SYK inhibitor to date, produces clinical response in ITP patients, including those who are refractory to other treatments. It appears to reduce the risk of thrombotic events and may therefore be a drug to consider for patients with an increased thrombotic risk. Encouraging results have also been obtained in the treatment of warm autoimmune hemolytic anemia. Several other SYK inhibitors have entered clinical trials for a range of indications, reflecting the ability of these drugs to affect multiple signaling pathways. SYK inhibitors have the potential to target several aspects of COVID-19 pathogenesis including thrombosis, without affecting normal hemostasis, and data from the first study of fostamatinib in COVID-19 are encouraging. It is hoped that ongoing trials in autoimmune indications other than ITP, as well as in hematological malignancies and other disorders, confirm the promise of SYK inhibitors.

Plain Language Summary

Immune thrombocytopenia (ITP) is an autoimmune disease that usually happens when your immune system mistakenly attacks and destroys platelets, which are cells that help blood to clot. Individuals with ITP can experience easy or excessive bruising and bleeding. Scientists have identified that an enzyme called spleen tyrosine kinase (SYK) is involved in numerous biological processes that are associated with the immune system response, inflammation, and some types of cancer in humans. Therefore, it has become a target for new drugs which inhibit the action of SYK. In this review article, the authors provide a summary of the biological properties and actions of SYK and its involvement in various diseases, discuss information about drugs that have been developed as SYK inhibitors for the treatment of ITP, and consider other potential uses for drugs that inhibit SYK. Although several drugs are being developed, the only SYK inhibitor that is currently available for the treatment of ITP is a drug called fostamatinib. In patients with ITP, including those who no longer respond to other treatments, fostamatinib has been shown to improve platelet counts and reduce bleeding events. Researchers are also currently investigating the use of drugs that inhibit SYK, including fostamatinib, for the potential treatment of other diseases associated with inflammation (e.g. rheumatoid arthritis, COVID-19), autoimmunity (e.g. warm autoimmune hemolytic anemia), and blood cancers (e.g. lymphoma, chronic lymphocytic leukemia, and acute myeloid leukemia).

Keywords
Cevidoplenib, entospletinib, fostamatinib, HMPL-523, spleen tyrosine kinase, SYK

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Introduction

Spleen tyrosine kinase (SYK) is expressed primarily in hematopoietic cells. SYK binds to immune receptors, such as B-cell receptors (BCR), Fc receptors (FcR), and C-type lectin receptors (CLR), or the associated adaptor proteins carrying immunoreceptor tyrosine-based activation motifs (ITAMs). SYK activation mediates diverse biological processes, including production

and secretion of cytokines, phagocytosis of autoantibody-coated cells, osteoclast maturation, and regulation of platelet aggregation. SYK is also involved in the release of neutrophil extracellular traps (NETosis) [1].

SYK's role in these processes makes it a potentially important target in a number of diseases with an immune-mediated pathogenesis. Fostamatinib, the only SYK inhibitor currently approved for use, is approved for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments [2]. Fostamatinib and several other SYK inhibitors including entospletinib, lanraplenib, HMPL-523, GSK2646264, and cevidoplenib are currently under investigation in clinical trials for a range of indications, including autoimmune diseases such as ITP, systemic lupus erythematosus (SLE), and warm autoimmune hemolytic anemia (wAIHA), as well as cancers including B-cell lymphomas and acute myeloid leukemia (AML) (Table I) [3]. More recently, a trial involving inflammatory signal inhibitors (including the SYK inhibitor fostamatinib) has been initiated in patients with mild-to-moderate COVID-19 and the results are awaited with interest [4].

This narrative review summarizes SYK biology and involvement in disease pathways, provides an update on SYK inhibitors in the treatment of ITP, and considers other potential applications of SYK inhibition including in patients with COVID-19.

Spleen tyrosine kinase (SYK) in human biology and disease pathways

SYK is a cytoplasmic nonreceptor-type protein tyrosine kinase that comprises a kinase domain (KD) located at its COOH terminus, and two SH2 domains (SH2-N and SH2-C) located at its NH2 terminus, separated by interdomain regions [5,6]. In the resting state, SYK is autoinhibited. Upon stimulation, the tandem SH2 domains of SYK bind to phosphorylated ITAMs causing conformational changes that result in the activation of its kinase domain (for a review see Mócsai et al [5]). SYK plays a key role in innate and adaptive immunity as well as other aspects of human biology, such as osteoclast maturation, and platelet activation. SYK plays a major role in the etiopathology of numerous autoimmune diseases, particularly those that are autoantibody-mediated, such as ITP, wAIHA, and rheumatoid arthritis (RA). SYK is also involved in hematological cancers, including follicular lymphoma, chronic lymphocytic leukemia (CLL), and AML [7]. Consequently, SYK inhibitors have a potential role in the treatment of these disorders as well as COVID-19–associated inflammation and coagulopathy.

SYK and the immune system

Receptor activity and downstream signaling

SYK plays a fundamental role in the immune system as the main activator of several key immune-related signaling pathways (Figure 1) [8], interacting with three major receptor types: FcRs, CLRs, and BCRs. In all three cases, SYK binds to ITAM and activates downstream signaling, initiating cellular processes that vary with cell type, including degranulation of mast cells and basophils; cytokine release from macrophages, monocytes and dendritic cells; and antigen recognition by B cells, leading to antibody production.

Activation of FcγRs on myeloid cells triggers a SYK-mediated signaling pathway resulting in internalization of IgG-opsonized antigens, cells, or pathogens by phagocytosis [9]. Immune complexes combining IgG autoantibodies bound to self-antigens on cells such as platelets and red blood cells can also activate FcγR, which occurs in autoimmune diseases such as ITP, wAIHA, RA, and SLE [8]. SYK is also involved in allergen-associated FcεR-triggered mast cell activation in hypersensitivity responses [8,10].

CLRs recognize tissue damage associated molecular patterns (DAMPS) as well as pathogen-associated molecular patterns (PAMPS) and are therefore implicated in sensing both infections and autoimmune diseases [5].

The BCR is an adaptive immune system receptor found on the surface of B cells. BCRs are linked to multiple signaling pathways by SYK phosphorylation of adaptor proteins, and SYK plays a key role in the development and activation of B cells in response to BCR stimulation [8]. Inappropriate and disordered activation of these pathways can lead to development of B-cell lymphomas and leukemia [10].

Table I. SYK inhibitors under evaluation in clinical trials [3].

Drug	Formulation	Diseases Studied
Fostamatinib	Oral	**ITP**: Approved **RA**: Phase 3 [NCT01197534, NCT01197521, NCT01197755, EudraCT 2010–020744–35, EudraCT 2010–020743-12] **wAIHA**: Phase 3 [NCT03764618, EudraCT 2018–004774-97] **CLL**: Phase 2 [NCT00446095, EudraCT 2009–009034-32] **COVID-19**: Phase 3 [NCT04629703, NCT04924660, EudraCT 2020–001750-22] **Other diseases**
Entospletinib	Oral	**B-cell lymphoma**: Phase 2 [NCT02568683, NCT03225924, EudraCT 2016–003103–56, EudraCT 2015–002731-17] **Hematologic malignancies (leukemia, lymphoma)**: Phase 2 [NCT01796470, NCT01799889, NCT03010358] **AML**: Phase 3 [EudraCT 2021–000761-33] **CLL**: Phase 2 [EudraCT 2016–002768-15]
HMPL-523	Oral	**B-cell lymphoma**: Phase 1 [NCT03779113, NCT02857998] **ITP**: Phase 3 [NCT05029635]
GSK2646264	Cream	**Urticaria**: Phase 1 [NCT02424799] **CLE**: Phase 1 [NCT02927457]
Lanraplenib	Oral	**Sjögren's syndrome**: Phase 2 [NCT03100942] **CLE**: Phase 2 [NCT03134222] **LMN**: Phase 2 [NCT03285711] **AML**: Phase 2 [NCT05028751]
Cevidoplenib	Oral	**RA**: Phase 2 [EudraCT 2018–003330-32] **ITP**: Phase 2 [EudraCT 2018–003329-26]

AML = acute myeloid leukemia, CLE = cutaneous lupus erythematosus, CLL = chronic lymphocytic leukemia, ITP = immune thrombocytopenia, LMN = lupus membranous nephropathy, RA = rheumatoid arthritis, wAIHA = warm autoimmune hemolytic anemia.

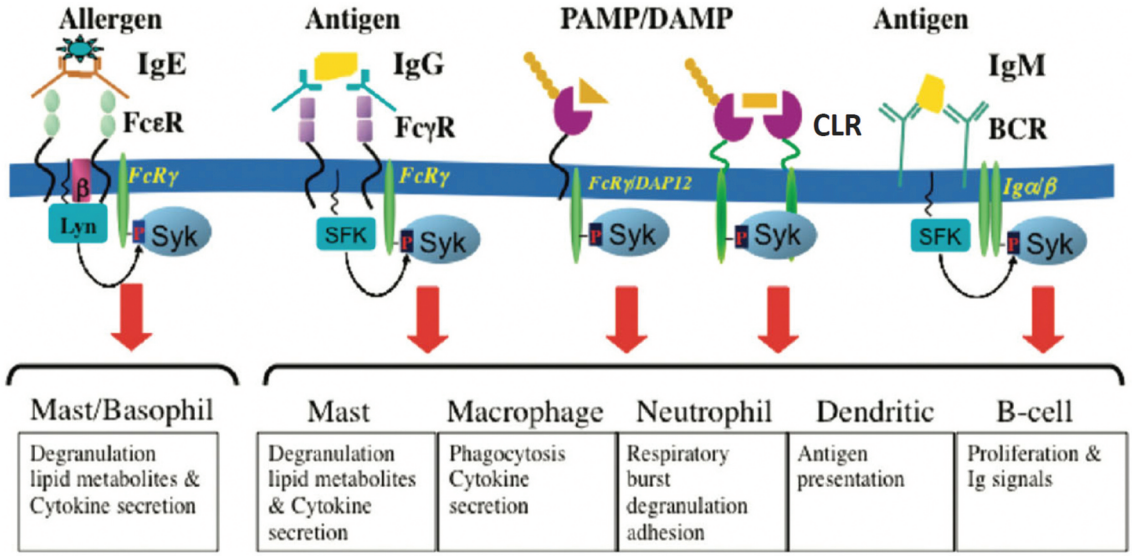

Figure 1. Role of SYK in key signaling systems involved in the immune system. Reproduced with permission from [8].

SYK is also expressed in various nonimmune system cells, where it is involved in a range of activities, including cellular differentiation and adhesion [6]. For example, SYK is necessary for osteoclast development and functioning, and is involved in regulation of lymphatic endothelial cell functioning [5,6].

SYK inhibition

Most of the investigation of SYK inhibition has been performed with fostamatinib or its active metabolite R406. Fostamatinib is a prodrug that is converted to the active compound R406 in the gastrointestinal tract [11]. R406 is a potent inhibitor of SYK kinase activity, acting in an ATP-competitive manner [12]. Detailed characterization of biochemical and cell-based activity of R406 toward SYK is available in Braselmann et al [12]. The inhibitor is equipotent against rodent and human SYK both biochemically and in cell-based assays.

As a potent SYK inhibitor, R406 is a powerful tool for investigating SYK biology. In *in vitro* experiments, R406 inhibited FcγR-mediated mast cell activation and subsequent degranulation (measured as tryptase release, EC_{50} 0.043–0.053 μM), FcγR-mediated neutrophil activation (via oxidative burst assay, EC_{50} 0.030 μM), FcγR-macrophage activation and subsequent release of cytokines (TNFα release EC_{50} 0.085 μM), and BCR-mediated B-cell upregulation (measured as CD69 upregulation, EC_{50} 0.048 μM) [12].

SYK is situated at the top of a number of signaling cascades and serves as an ideal target for modifying autoimmune disease [10]. Blocking SYK with R406 results in silencing of various kinases that have been implicated in autoimmune diseases and cancers, including Akt/protein kinase B, multiple mitogen-activated protein (MAP) kinases, phospholipase C γ (PLCγ) and Bruton's tyrosine kinase (BTK) [12].

Animal models of SYK inhibition

SYK inhibition has been shown to ameliorate antibody-mediated pathology in a number of rodent disease models, including vasculitis, arthritis, ITP, AIHA, glomerulonephritis and acute lung injury. R406 reduced immune-complex–mediated inflammation in a reverse passive Arthus reaction vasculitis model in mice [12]. R406 also mitigated collagen-antibody–induced arthritis and K/BxN serum-induced arthritis in mice [12,13]. Treatment with R406 reduced the severity of glomerular injury in rats with nephrotoxic serum-induced nephritis (glomerulonephritis model) [14]. In murine models of ITP and AIHA, pretreatment with R406 protected animals from developing thrombocytopenia and anemia, respectively, with an effect comparable to that seen with intravenous immune globulin (IVIg) [15,16].

In other animal models, SYK inhibition with R406 ameliorated chronic diseases with a strong autoimmune component, such as SLE, type 1 diabetes, atherosclerosis, inflammatory bowel disease, multiple sclerosis, and asthma [17–20].

Findings in humans

A recent study identified six patients with gain-of-function SYK mutations that resulted in systemic inflammation due to constitutive SYK activation [7]. Multiple organs were impacted, including skin, intestines, joints, lungs, central nervous system, and liver. The patterns of inflammation observed in these patients were consistent with those seen in the animal models of SYK-mediated diseases. These findings provide a roadmap for diseases that may be driven by SYK in humans, such as inflammatory bowel disease, psoriatic diseases, RA, acute lung injury, acute respiratory distress syndrome (ARDS), neuroinflammation (e.g. multiple sclerosis), nonalcoholic and alcoholic steatohepatitis, and lymphoma (CLL, follicular lymphoma) [7].

SYK inhibition and specific disease pathways

Rheumatoid arthritis

Introduction of one of the SYK gain-of-function mutations identified in humans (SYK-S544Y) into mice resulted in early development of severe arthritis due to excessive osteoclastogenesis [7]. The role of dysregulated osteoclast differentiation and contribution to the observed erosive arthritis was confirmed by *ex vivo* experiments. SYK inhibition with R406 prevented osteoclast differentiation improved arthritis scores in the SYK-S544Y gain-of-function mice.

SYK inhibition also targets other aspects of RA pathology due to the effects on cytokine production by macrophages, neutrophil, and mast cell activation, autoantigen presentation to T cells by innate

immune system cells, and other, indirect effects on the adaptive immune system [21].

Immune thrombocytopenia and warm autoimmune hemolytic anemia

The mechanisms of disease for ITP and wAIHA are similar, involving phagocytosis of platelets or RBCs targeted for destruction by anti-platelet or anti-RBC antibodies, respectively. It was later established that SYK-mediated phagocytosis of opsonized platelets by macrophages is an important mechanism of ITP pathogenesis [22]. Experimental evidence from SYK knockout (Syk -/-) macrophages has led to the observation that SYK inhibition can prevent the phagocytosis and destruction of platelets. In the presence of opsonized RBCs, wild-type macrophages engulf the RBCs, whereas opsonized RBCs attached to the surface of Syk -/- macrophages are not phagocytosed [23].

Animal studies have provided additional evidence for this mechanism. For example, mice injected with an antiplatelet antibody (mAB 6A6) developed severe thrombocytopenia; however, FcRγ-deficient mice did not, suggesting that murine ITP is dependent on FcRγ signaling and, by extension, on the SYK activity downstream of the FcRγ receptor that leads to platelet loss via phagocytosis [24].

This observation can be mimicked *in vitro* using a SYK inhibitor. When RBCs opsonized with antibody were exposed to human monocytic THP1 cells, up to 64% of the RBCs were phagocytosed. However, in the presence of R406, minimal phagocytosis of the antibody-coated RBCs occurred, similar to that seen with unopsonized RBCs. This result further supports the involvement of SYK signaling in antibody-mediated phagocytosis [Rigel unpublished data].

Thrombosis

SYK inhibition is a novel approach to targeting thrombosis through inhibition of platelet activation. SYK is expressed in platelets, with ligation of three receptors, GPVI, CLEC2, and FcγRIIA, leading to SYK-mediated signaling [8]. All three receptors are involved in thrombosis while playing negligible roles in hemostasis, and fostamatinib targets these three platelet receptors without affecting others involved in hemostasis such as the protease-activated receptor-1 (PAR1) for thrombin and the ADP receptor $P2Y_{12}$ [25]. In *in vitro* experiments, R406 inhibited FcγRIIA-mediated platelet aggregation induced by heparin-induced thrombocytopenia (HIT) sera, GPVI-mediated platelet aggregation induced by collagen, and CLEC2-mediated platelet aggregation induced by podoplanin, but had no effect on ADP-mediated platelet aggregation. Thus, R406 inhibited signaling via the receptors that are involved in thrombosis, leaving hemostasis-specific signaling unaffected [26,27].

While combined antibody-mediated depletion of GPVI and CLEC2 results in severe disruption of hemostasis reflected in dramatic increase in tail bleeding time [28], genetic ablation of both receptors is not as severe in bleeding prolongation, pointing at additional risk associated with the use of antibodies targeting the receptors. SYK knock out has even milder tail bleeding phenotype [29]. Finally, *in vivo* testing of two unrelated SYK inhibitors – PRT060318 [30] and BI1002494 [29] – at doses that dramatically affect thrombosis was not associated with any increase in bleeding time in mice. In line with that, *in vivo* use of R406, an active metabolite of fostamatinib, did not result in bleeding time prolongation in mice [12]. Finally, testing fostamatinib in healthy volunteers at doses that are much higher than those typically prescribed to ITP patients did not affect platelet aggregation *ex vivo* [12]. Thus, evidence indicates that SYK inhibition increases hemostasis while potentially reducing the risk of thrombosis.

In vivo, SYK inhibition similarly decreased thrombosis in animal models, without affecting hemostasis. In the presence of the SYK inhibitor BI1002494, the time to occlusion was prolonged (reflecting reduced thrombosis), with no increase in bleeding time (reflecting no effect on hemostasis) [29].

COVID-19

Early pathologies of SARS-CoV-2-related respiratory diseases involve infection of bronchial epithelial cells, alveolar pneumocytes and capillary endothelial cells, following interaction between the spike protein and the cell surface angiotensin-converting enzyme 2 (ACE2) receptor [31]. Penetration of the virus into host cells results in an immune response typified by the release of inflammatory cytokines from infected cells and alveolar macrophages, as well as activation and recruitment of T lymphocytes, monocytes, and neutrophils [32,33]. The role of the vascular endothelium has become increasingly recognized, with endothelial damage contributing to the inflammatory milieu [34]. A dysfunctional endothelium promotes coagulopathy leading to the formation of microthrombi and subsequent thrombotic sequelae such as diffuse intravascular coagulation (DIC) and thrombocytopenia; these deleterious effects increase vascular permeability in the lungs and contribute to pulmonary edema [34–37]. There is also evidence of enhanced NETosis in hospitalized patients with COVID-19 and this has been shown to trigger and propagate inflammatory cytokine release, thrombosis, and cell damage [38–40].

During COVID-19 disease progression, CLRs and FcγRs on the surface of platelets, macrophages, dendritic cells, and neutrophils are activated by viral antigen antibody immune complexes that trigger an intracellular signaling cascade dependent on SYK recruitment [10,41,42]. The resulting cytokine storm, coagulopathy, and NETosis potentiate disease severity and this is targetable with SYK inhibitors, potentially modifying the severity of COVID-19 infection (Figure 2) [43]. In preclinical studies, SYK inhibition protected mice against LPS-induced acute lung injury and thrombosis [29,44]. *In vitro* studies with COVID-19 plasma demonstrated that the use of a SYK inhibitor abrogated the hyperimmune response triggered by anti-spike IgG, inhibited platelet hyperactivation, and blocked NETosis [45–47]. Thus, SYK inhibition has the potential to target multiple aspects of COVID-19 pathogenesis. The specific mechanisms by which SYK inhibition could potentially modify the severity of COVID-19 infection, including a reduction in mucus production, inhibition of proinflammatory pathways, and inhibition of thrombo-inflammation are discussed in the following sections.

Excess mucus production. Excess mucus is linked to adverse outcomes in respiratory diseases, and elevated levels of MUC1 (a mucin-producing epithelial transmembrane protein) predicts development of acute lung injury and ARDS. Fostamatinib was shown to reduce MUC1 in a mouse model and was identified from a repurposing library as a candidate treatment for acute lung injury, including COVID-19 [48,49].

Hyperinflammation in response to viral antigens and COVID-19 immune complexes. High levels of pro-inflammatory cytokines are seen in severe COVID-19, and CRP is a predictor of mortality in COVID-19 patients age ≥60 years [50]. A number of small molecule inhibitors developed for RA, most of which target various types of kinases that are essential in downstream signaling of proinflammatory molecules, may be of benefit in COVID-19 infection [51]. Clinical trials have reported the potential benefit of Janus kinase (JAK) inhibitors in hospitalized adults with COVID-19 [52–54], although there are some toxicity concerns

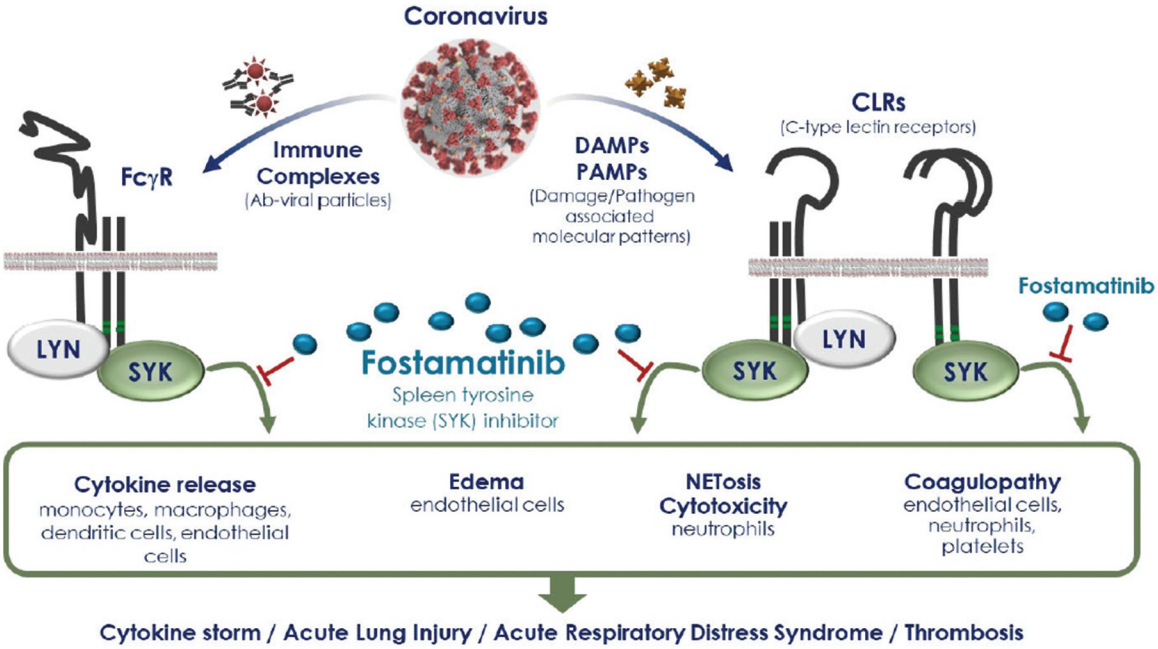

Figure 2. Role of SYK in the pathogenesis of COVID-19 and potential targets for SYK inhibitors [43].

for JAK inhibitors used to treat certain chronic inflammatory conditions [55].

Inhibition of SYK signaling with R406 protects against LPS-induced acute lung injury in animal models, preventing ARDS-like pathology in the lungs of mice and improving their survival compared with controls. This protective effect is likely due to blockade of neutrophilic airway inflammation, vascular permeability, pro-inflammatory cytokine release, and oxidative stress in innate immune cells [44]. Furthermore, *in vitro* studies have shown that anti-SARS-CoV-2 IgG (anti-spike) from the sera of severely ill COVID-19 patients promotes macrophage hyperinflammatory responses, which in turn leads to endothelial disruption and platelet endothelial adhesion. The hyperinflammatory responses were blocked by R406 [45,56].

COVID-19–associated thrombosis/coagulopathy. SYK inhibition may abrogate thrombo-inflammation via two separate mechanisms, inhibition of platelet activation and inhibition of NETosis. SYK mediates signaling downstream of GPVI/FcRγ and the CLEC-2 receptor, which leads to platelet activation [25,57]. As noted previously, these signaling pathways are inhibited by R406. Recent *in vitro* modeling found evidence that pulmonary immune complexes may activate platelets and contribute to thrombosis in COVID-19. Immune complexes of spike protein and anti-spike IgG enhanced platelet-mediated thrombosis on von Willebrand factor, a process that occurred when the IgG Fc domain glycosylation profile was modified to correspond with that seen in patients with severe COVID-19 [58]. This platelet activation was dependent on FcγRIIA and was inhibited by R406. It has also been found that R406 ameliorated platelet aggregation induced by serum from patients with severe COVID-19 in a hematoporphyrin-induced photochemical injury model in an endothelial-lined microfluidic channel [46]. This evidence implicates FcR-mediated platelet aggregation in COVID-19-associated thrombosis and indicates it can be abrogated by SYK inhibitors.

SYK inhibition potentially alleviates COVID-19–associated thrombosis and thrombo-inflammation via inhibition of NETosis. NETosis is the immune system's first-line defense system involving neutrophils which release web-like NETs, consisting of chromatin, histones, and antimicrobial proteins, which trap and kill microbes [59]. NETs can also bind activated platelets, RBCs, and leukocytes, and can cause endothelial dysfunction, as well as tissue damage, especially lung damage, and coagulopathy [60,61]. In addition, they have proinflammatory and prothrombotic effects, including activation of dendritic cells and promotion of platelet aggregation. NETosis can be induced by immune complexes in autoimmune disease and also contribute to sepsis and ARDS pathogenesis with vascular tissue damage and microthrombi [62].

NETosis has been shown to increase in severe COVID-19, with pulmonary autopsies confirming NET-containing microthrombi with neutrophil/platelet infiltration [62]. Patients with severe COVID show pathology similar to that seen in patients with HIT and experiments in a transgenic mouse model showed that HIT-mediated thrombosis can be prevented by inhibiting SYK [63]. HIT is driven by immune complexes activating both platelets and neutrophils through FcγRIIA, resulting in NETosis and thrombosis. Interestingly, similar mechanisms have been hypothesized to be involved in the pathogenesis of vaccine-induced thrombotic thrombocytopenia (VITT) [64–66]. VITT is a rare (2 per 100 000 first-dose vaccinations), but serious, syndrome characterized by thrombocytopenia, thrombosis, a markedly raised D-dimer, and the presence of anti-platelet factor-4 (PF4) antibodies following COVID-19 adenovirus vaccination. The underlying mechanisms responsible for VITT are not fully understood, but it has been postulated that they are the result of an idiosyncratic immune response directed against PF4 in complex with a component of the adenoviral

vaccine. Similarly, why VITT is so rare remains an unanswered question [64].

Severe COVID-19 is usually associated with seroconversion-producing neutralizing antibodies; the subsequent process is then similar to that of HIT, with activation of neutrophils and induction of NETosis, and activation of platelets. Therefore, HIT-like thrombosis in severe COVID-19 patients may be a sign of FcγRIIA-mediated NETosis of neutrophils and platelet activation [67–69]. Since immune complexes induce NETosis via binding of FcγRs through SYK-mediated signaling, this process can be blocked by SYK inhibition [70]. *In vitro* data have shown that R406 inhibits NETosis induced by plasma from COVID-19 patients [47].

Update on clinical trials with SYK inhibitors in ITP

Six SYK inhibitors are now being evaluated in clinical trials across a variety of indications, including B-cell lymphomas; AML; various autoimmune diseases, such as ITP, systemic lupus erythematosus (SLE), and wAIHA; and, more recently, COVID-19. The range of diseases being studied reflects the multifunctionality of SYK, including importance in the B-cell development pathway. Key findings from clinical trials with SYK inhibitors in ITP are summarized in this section. Clinical trials in other indications are discussed in a later section.

Fostamatinib was approved in 2018 in the US for adult patients with chronic ITP and an insufficient response to a prior treatment [71] and, in 2020, was approved in the EU for the treatment of chronic ITP in adult patients who are refractory to other treatments [2]. Other SYK inhibitors currently being evaluated in ITP include HMPL-523 (phase 1; NCT03951623) [72] and cevidoplenib (phase 2; NCT04056195) [73]; clinical results are not yet available for HMPL-523 [74]. Differences between the various SYK inhibitors have not been evaluated as no comparative studies have been completed.

Fostamatinib in ITP

SYK inhibition prevents platelet destruction through inhibition of FcγR signaling in macrophages and may inhibit BCR signaling that leads to plasma cell formation and autoantibody production. These functions make SYK inhibition an interesting therapeutic approach for ITP, because of the potential to target both aspects of ITP – autoantibody-mediated destruction of platelets by macrophages as well as autoantibody production.

A noncomparative phase 2 study, two placebo-controlled phase 3 studies, and an open-label extension study have been conducted with fostamatinib in adult patients with ITP (Table II). The results indicated that fostamatinib improved platelet counts and reduced

Table II. Completed clinical trials of fostamatinib in immune thrombocytopenia.

Study	Treatment (mg)	Main endpoint	Main results
Phase 2 open-label [15]	FOS 75–175 bd (escalation) (3–53 wk) (N = 16)	Platelet response (↑ in platelet count by >20x10^9/L to ≥30x10^9/L with no rescue therapy)	12/16 pts (75%) showed a response. 8/16 (50%) had a sustained response with platelets >50x10^9/L at 95% of visits. Most common AEs: gastrointestinal (eg, diarrhea, vomiting).
Phase 3 pooled analysis (FIT-1/FIT-2) [75]	FOS 100–150 bd (N = 101) PL (N = 49) (24 wk)	Stable platelet response by wk 24 (≥50x10^9/L on ≥4/6 visits between wk 14 and 24 with no rescue therapy); Post hoc: overall response (platelet count ≥50x10^9/L between wk 1 and 12)	Stable response in 18% on FOS vs 2% on pbo (p = .0003). Overall response seen in 43% on FOS vs 14% on pbo (p = .0006). Rescue medication received by 30% on FOS vs 45% on pbo (p = .07). Moderate/severe bleeding events seen in 9% overall responders/6% stable responders on FOS vs 16% on PL. Most common AEs (FOS): diarrhea, nausea, hypertension, dizziness, increased ALT/AST.
Phase 3 Open Label Extension; pooled analysis (FIT-1/FIT-2/FIT-3) [75]	FOS 100–150 bd (N = 146) (median 6.7 months, range 1–31)	Stable platelet response (as above) for randomized pts. For patients initiating FOS in OLE: ≥1 count ≥50x10^9/L in first 3 months and at 2/3 subsequent visits).	Median duration of stable response >28 months. Median duration of overall response >28 months. 81% of stable responders maintained platelet counts at >50x10^9/L during OLE; overall responders generally maintained platelet counts at >30x10^9/L. No new or increased frequency of AEs seen up to 31 months.
Long-term follow-up of phase 3 studies; pooled analysis (FIT-1/FIT-2/FIT-3) [25]	FOS 100–150 bd (N = 146) (median treatment duration 19 months, range 1–61.7)	Platelet count ≥50x10^9/L and ≥30x10^9/L	54% achieved ≥1 platelet count ≥50x10^9/L (reached by wk 12 in 44%). 70% achieved ≥1 platelet count ≥30x10^9/L (by wk 12 in 63%). Among 36 pts still receiving FOS (median 49 months, range 42–62), 34 have platelet count ≥50x10^9/L.
Post hoc analysis of phase 3 studies; pooled analysis (FIT-1/FIT-2/FIT-3) [76]	FOS as second-line (n = 32) or third-or-later line (n = 113)	Response (platelet count ≥50x10^9/L)	78% of pts receiving second-line therapy with fostamatinib achieved ≥1 platelet count ≥50x10^9/L in and 48% of those on third-or-later line therapy achieved this response.

AE=adverse event, bd=twice daily, DB=double-blind, FOS=fostamatinib, OLE=open-label extension, pbo=placebo, pts=patients, wk=weeks.

bleeding events compared with placebo, with a trend toward decreased use of rescue medication [15,25,75–77]. Overall response rates were 37–48% for fostamatinib versus 8–21% for placebo [10]. Platelet counts increased rapidly, with a median time to first platelet response of 2 weeks [77]. Responses were durable, being maintained for a median of >28 weeks in the interim analysis of the open-label extension study [75], with some patients still showing a response up to 5 years [25].

A *post hoc* analysis of phase 3 data found that fostamatinib demonstrated enhanced efficacy when administered as second-line therapy, with 78% of patients achieving a platelet response $\geq 50 \times 10^9$/L compared with 48% when given as third or later lines [76]. Consistent with these response rates was the finding that bleeding events were less common in patients who received fostamatinib as second line versus later lines of therapy. This is consistent with the findings that major bleeding events seldom happen in patients with platelet counts ≥20–30×10^9/L [78].

A phase 4 observational study of fostamatinib as second-line therapy for ITP is now underway (NCT04904276) and in addition to measuring platelet response over time, the safety of fostamatinib will be evaluated (adverse event monitoring) as will treatment satisfaction and quality of life [79].

Safety and tolerability of fostamatinib in ITP

Fostamatinib was, generally, well tolerated in patients with ITP in clinical trials and a long-term extension study [11]. The most common adverse events included gastrointestinal disorders (such as diarrhea), hypertension and elevated transaminases. Most were mild or moderate in severity and were manageable with appropriate treatment or dose modification/interruption; few patients required permanent discontinuation of fostamatinib. The safety profile of fostamatinib in ITP was consistent with its profile in other indications such as RA [11].

Fostamatinib and thromboembolic events

Paradoxically, ITP is associated with an increase in both venous and arterial thrombosis [80]. One of the potential complications associated with the treatment of ITP particularly with splenectomy and TPO-RAs is an increased rate of venous (and to a lesser extent arterial) thromboembolic events, which can make management of the disorder challenging [81–83]. A recent meta-analysis on the risk of thrombosis with TPO-RAs compared to placebo or standard of care, found that more thromboembolic events were noted in the TPO-RA group than in the control group [84]. Most of the relative risk ratios also showed increased thrombosis with TPO-RA use; however, none of these risk ratios appeared to be statistically significant. Interestingly, there is some evidence that SYK inhibition may decrease the incidence of thrombosis. An analysis of the fostamatinib studies in ITP demonstrated a lower rate of thrombotic events compared with the rates observed for other ITP therapies [85]. In phase 3 studies (up to 5 years of treatment), there was only one reported thromboembolic event (TEE) among 146 patients (0.7%), a transient ischemic attack that resolved spontaneously [24]. In thrombopoietin receptor agonist (TPO-RA) studies, however, TEEs were reported in 0–9.4% of ITP patients receiving TPO-RAs in studies of up to 7 months' duration and 2.6–8. 9% of patients in studies of 2–8 years [24]. Fostamatinib may therefore be a drug to consider for patients with an increased thrombotic risk, such as those with coronary artery disease, diabetes, advanced age or obesity. Indeed, in a recent *in vitro* study, R406 had synergistic effects with existing antiplatelet agents on atherosclerotic plaque-induced platelet activation [86].

Other applications of SYK inhibition

In addition to ITP, SYK inhibitors are being evaluated for other indications, with results available for clinical studies in B-cell lymphomas, wAIHA, RA and, recently, COVID-19 (Table I).

Clinical trials in hematologic oncology

SYK inhibition abrogates signaling through the BCR, and SYK inhibition has been evaluated in several clinical trials in patients with B-cell lymphoid malignancies (Table III) [87–91].

Fostamatinib in B-cell lymphomas

Fostamatinib was the first drug to demonstrate the therapeutic potential of inhibiting BCR signaling in B-cell lymphomas. An open-label phase 1/2 study of fostamatinib in patients with relapsed/refractory B-cell lymphomas demonstrated significant clinical benefit in non-Hodgkin's lymphoma (NHL) and CLL. Notably, 55% of patients with CLL (n = 6/11) experienced a > 50% reduction in lymph node size, with median progression-free survival (PFS) of 6.4 months [87]. Fostamatinib 200–250 mg twice daily demonstrated safety and tolerability similar to that seen in large RA studies that used lower doses. A phase 2 study found that fostamatinib 100 or 200 mg twice daily was of limited clinical benefit in patients with diffuse large B-cell lymphoma of germinal center B-cell or intermediate cell of origin [88]. However, follow-up data for two patients documented a durable response to fostamatinib for over 6 years [89].

Entospletinib in B-cell lymphomas

Entospletinib is also undergoing trials in B-cell lymphomas [90,91]. A phase 2 study found that it showed clinical activity in patients with relapsed/refractory CLL, with acceptable toxicity [90]. A > 50% reduction in lymph node size was seen in 24/39 (61%) evaluable patients, and median PFS was 13.8 months [92]. Efficacy results for patients with other types of B-cell lymphoma enrolled in the study have not yet been reported.

Entospletinib in acute myeloid leukemia

Entospletinib was evaluated in a phase 1b/2 trial in patients with previously untreated *de novo* or secondary AML and was well tolerated [89]. Patients with mutations in *NPM1, FLT3-ITD*, and *KMT2A* had a higher response rate than other patients; all three of these AML subsets are associated with overexpression of *HOXA9* and *MEIS1*. This suggests that some AML subtypes may be more sensitive to SYK inhibition than others.

A phase 3, placebo-controlled study of entospletinib for *NPM1*-mutated AML is underway.

Fostamatinib clinical trials in rheumatoid arthritis

Thirteen phase 2/3 studies of fostamatinib in RA (including randomized, double-blind, placebo-controlled trials, and open-label studies) have established its safety profile in >3500 patients with up to 7 years of treatment [93–95]. A significant improvement was seen in a number of important clinical efficacy endpoints in these studies. In particular, fostamatinib 100–150 mg demonstrated significant improvements in tender and swollen joints of ≥20% (ACR20), ≥50% (ACR50) or ≥70% (ACR70) compared with placebo. In a meta-analysis, response rates were 48.0% for fostamatinib versus 32.8% for placebo for ACR20 ($p = .0004$), 26.4% versus 12.5% for ACR50 ($p < .00001$), and 12.7% versus 4.4% for ACR70 ($p < .00001$) [94]. A significant effect on ACR20 response to fostamatinib

Table III. Completed clinical trials of SYK inhibitors in hematologic malignancy.

Study	Treatment (mg)	Main endpoints	Main results
B-cell lymphoma			
Fostamatinib Phase 1/2, OL; relapsed/refractory B-cell lymphomas [87]	**Phase 1**: FOS 200 or 250 bd (N = 13) **Phase 2**: FOS 200 bd (N = 68)	ORR PFS	**Efficacy in Phase 2**: ORR was 55% (6/11) for SLL/CLL, 22% (5/23) for DLBCL, 10% (2/21) for FL, and 11% (1/9) for MCL. Median PFS was 6.4 months for SLL/CLL, 2.7 months for DLBCL, and 6.4 months for FL. **Phase 1/2**: Most common AEs were diarrhea, fatigue, cytopenias, hypertension, nausea.
Phase 2, r, db; relapsed/refractory DLBCL [88]	FOS 100 (N = 21) or 200 (N = 47) bd	ORR	**Efficacy**: ORR 3% in both arms; clinical benefit (≥ stable disease) 13% in both arms. Pts with clinical benefit from FOS had DLBCL of germinal center B-cell or intermediate cell of origin. **Safety in all pts**: most common AEs were diarrhea, and fatigue.
Case report (2 pts with DLBCL from the Phase 2 study) [89]	Pt A: FOS 100 bd then 100 od Pt B: FOS 200	CR and PR	Pt A: CR maintained for >5 years. Pt B: PR since Dec 2014 with a continued sustained metabolic response for >6 years.
Entospletinib Phase 2, OL; relapsed/refractory non-Hodgkin's B-cell lymphomas [90]	ENT 800 bd (N = 186 including CLL N = 41)	PFS rate at 24 wk	**Efficacy in CLL**: ORR 61.0%; 24-wk PFS rate 70.5%, median PFS 13.8 months, **Safety in all pts**: most common AEs were dyspnea, pneumonia, febrile neutropenia, dehydration, pyrexia.
Acute myeloid leukemia			
Entospletinib Phase 1b/2, OL; treatment-naïve AML [91]	**Phase 1b**: ENT 200 or 400 bd + chemotherapy **Phase 2**: ENT 400 bd + chemotherapy	Composite CR	Composite CR rate 70%. Pts with above median *HOXA9* and *MEIS1* expression had better overall survival than pts with below median expression. Most common AEs were cytopenias, febrile neutropenia, infection.

AE=adverse event, AML=acute myeloid leukemia, bd=twice daily, CLL=chronic lymphocytic leukemia, CR=complete response, DLBCL=diffuse large B-cell lymphoma, ENT=entospletinib, FL=follicular lymphoma, FOS=fostamatinib, MCL=mantle cell lymphoma, od=once daily, OL=open-label, ORR=objective response rate, PFS=progression free survival, PR=partial response, pts=patients, SLL=small lymphocytic leukemia, wk=weeks.

was seen within 1 week. In addition, reductions in the levels of the interleukin-6 (a proinflammatory cytokine) and in matrix metalloproteinase 3 (an inflammatory mediator) were observed within 1 week of starting treatment with fostamatinib [96].

Overall, the data indicate that SYK inhibition significantly improved signs and symptoms of RA and reduced inflammation and cytokine release in synovial tissue.

With respect to safety, a recent meta-analysis of RA studies found no overall increased risk of neoplasms with fostamatinib use [97].

Fostamatinib clinical trials in warm autoimmune hemolytic anemia

Autoimmune hemolytic anemia is an acquired hemolysis caused by autoantibodies targeting RBC antigens. SYK inhibition can prevent RBC destruction through both inhibition of FcγR signaling in macrophages and inhibition of BCR signaling, leading to plasma cell formation and autoantibody production.

Preliminary results from the phase 2 SOAR study of fostamatinib in wAIHA (the predominant subtype of autoimmune hemolytic anemia) have been presented [98]. In this open-label, noncomparative study (NCT02612558), adults with primary or secondary wAIHA who had failed at least one line of treatment and had hemoglobin <10 g/dL were treated with fostamatinib 150 mg bid. The primary endpoint (hemoglobin >10 g/dL with an increase of ≥2 g/dL from baseline by week 24 without rescue therapy or RBC transfusion) was achieved in 11 of 24 evaluable patients (46%), with another patient experiencing a late response. Overall, 50% of patients gained clinical benefit. Among the 11 responders, six (55%) achieved a response within the first 2 weeks (Figure 3). The most common adverse events were diarrhea, fatigue, hypertension, and dizziness [98].

A phase 3, randomized, double-blind, placebo-controlled, 6-month trial of fostamatinib for wAIHA has completed enrollment and an open-label extension study is ongoing (NCT03764618) [99,100]. The initial dose of fostamatinib is 100 mg twice daily, titrated to 150 mg twice daily if tolerated. Preliminary data on baseline characteristics suggest patients are similar to those enrolled in the phase 2 study.

Fostamatinib clinical trials in COVID-19

Recently, fostamatinib has been evaluated in patients with COVID-19, with three phase 2 or 3 studies underway and one phase 2 study completed.

NIH/NHLBI clinical trial in COVID-19

The US NIH/NHLBI with INOVA have conducted a double-blind, placebo-controlled phase 2 study of fostamatinib (both arms included standard of care [SOC], primarily dexamethasone and remdesivir) for hospitalized adults with COVID-19 requiring supplemental oxygen (NCT04579393) [101]. Study endpoints included the incidence of serious adverse events at day 29 (primary endpoint), mortality at day 29, median number of days in ICU, and inflammatory biomarker levels associated with COVID-19.

Fostamatinib was shown to be well tolerated in hospitalized patients with COVID-19 on oxygen. The trial met its primary endpoint of safety, with no significant increase in serious adverse events with the addition of fostamatinib to standard of care ($p = .2$); in fact, serious adverse events occurred in half as many patients in the fostamatinib group (10.5%) in comparison with the placebo group (22.0%). No deaths occurred among the 30 patients in the fostamatinib group, and three deaths occurred among the 29 patients in the placebo group ($p = .07$). A greater improvement in clinical status by day 15 ($p = .035$) was seen with fostamatinib. The median number of days in ICU was 3

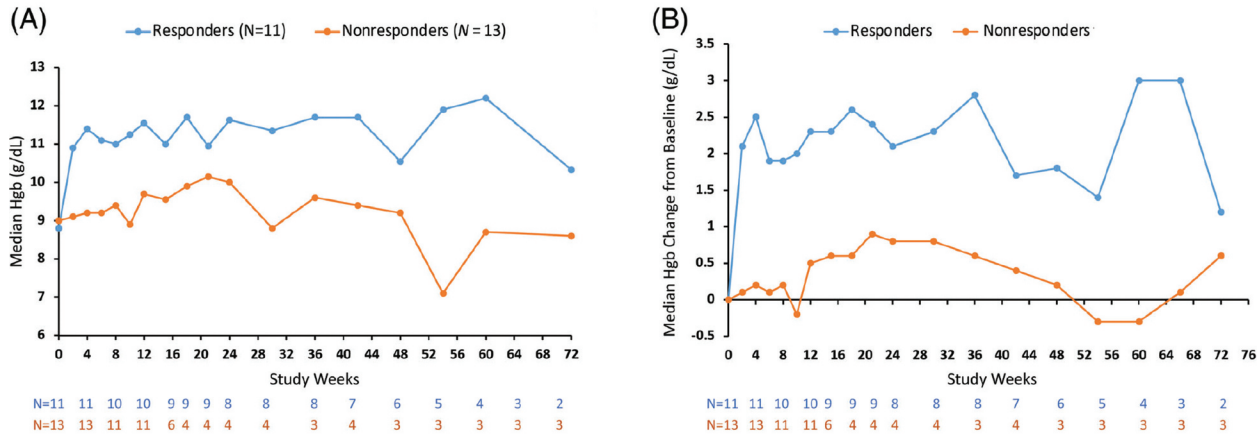

Figure 3. Fostamatinib improves markers of red cell hemolysis in warm autoimmune hemolytic anemia: (a) median hemoglobin (Hgb) in the efficacy evaluable population (n = 24) categorized by response and (b) median change in Hgb from baseline in the efficacy evaluable population (n = 24) categorized by response [98].

with fostamatinib versus 7 with placebo ($p = .07$). Reductions in NETosis and inflammatory markers were also noted [101].

MATIS clinical trial in COVID-19

The MATIS trial is a two-stage, open-label, randomized, controlled, phase 2 study of ruxolitinib or fostamatinib (both arms include SOC) compared to SOC alone in hospitalized patients with COVID-19 pneumonia [4]. This UK study is designed to assess any reduction in the number of hospitalized patients who develop more severe disease and progress to ICU. Mortality and the requirement for ventilation will also be assessed. It is planned to enroll 171 patients in stage 1, and 285 in stage 2 (if at least one experimental intervention in stage 1 shows promise).

FOCUS phase 3 clinical trial in COVID-19

The third study is a double-blind, randomized, placebo-controlled, adaptive, phase 3 study of fostamatinib plus SOC in the treatment of hospitalized adults with COVID-19 in the USA (NCT04629703), with a planned enrollment of 308 patients. Endpoints include progression to severe/critical disease within 29 days of the first dose of treatment, number of patients transferred to ICU, total number of days hospitalized, and mortality [43].

Novel experimental COVID-19 therapies affecting host response (NECTAR)

This study is a double-blind, randomized, placebo-controlled, phase 2/3 study with 4 active arms [TXA127, human peptide angiotensin-(1–7); TRV027, a selective AT_1 receptor agonist; fostamatinib, a SYK inhibitor; and APN01 (alunacedase alfa; a recombinant form of human angiotensin-converting enzyme 2) for the treatment of hospitalized adults with COVID-19 in the USA (NCT04924660), with a planned enrollment of 1600 patients. Endpoints include number of days without supplemental oxygen, number of patients free of supplemental oxygen at days 14 and 28 and mortality among other measures [102].

Conclusion

SYK activity is critical in multiple signaling pathways, mediating downstream events following activation of Fc receptors, resulting in phagocytosis and propagation of the inflammatory response and, in particular, FcγRIIA, resulting in release of nets from neutrophils; B-lymphocyte receptors, resulting in B-cell proliferation, differentiation, and activation; and GPVI, CLEC-2, and FcγRIIA receptors, resulting in platelet activation. Consequently, SYK plays a role in multiple autoimmune diseases (ITP, wAIHA, RA, IgA nephropathy) and hematologic cancers (follicular lymphoma, CLL, AML), and SYK inhibitors have been shown to modify these disease pathways. For example, SYK inhibitors alleviate inflammation by blocking Fc receptor and C-type lectin receptor signaling; alleviate arthritis by blocking osteoclastogenesis; block platelet and RBC destruction via inhibition of antibody-mediated phagocytosis in ITP and wAIHA, respectively; and target thrombosis without affecting hemostasis. SYK inhibitors may also alleviate complications of COVID-19 by blocking hyperinflammatory cytokine production by macrophages; abrogation of coagulopathy induced by platelet, neutrophil, and endothelial cell activation; and inhibition of NETosis by neutrophils.

Fostamatinib is the first SYK inhibitor approved for therapeutic use. It was approved for use in the treatment of chronic ITP based on efficacy demonstrated in phase 2/3 clinical trials. Fostamatinib provides rapid and durable increases in platelet counts in patients who are refractory to other therapies, as well as reductions in bleeding and use of rescue medication, without an increase in thrombotic risk. Other SYK inhibitors, including HMPL-523 and cevidoplenib, are currently being evaluated in ITP.

SYK inhibition is also a target for the treatment of a variety of other inflammatory, autoimmune, and neoplastic diseases. In phase 2/3 clinical trials, SYK inhibitors have shown activity/efficacy in wAIHA (phase 2), oncology (lymphoma, CLL and AML), RA, and COVID-19 (phase 2). Phase 3 studies are ongoing with fostamatinib for wAIHA and COVID-19 and with entospletinib for AML.

Expert opinion: SYK pathways and the future

SYK is an important regulatory molecule of signal transduction pathways involved in the pathogenesis of autoimmune diseases such as ITP, and the SYK-signaling pathway has emerged as a potential target for the treatment of such diseases. Platelet destruction in ITP is mediated by SYK-dependent phagocytosis of FcγR-bound platelets and inhibition of this step represents a promising approach to the management of ITP. SYK inhibitors have been investigated in clinical trials since 2007. Fostamatinib was approved for use in chronic ITP refractory to other treatment in 2018 in the US and at the beginning of 2020 in the EU and remains the only licensed SYK inhibitor to date. Recent results have shown that fostamatinib is well tolerated in the majority of patients, and it produces clinical response in ITP patients,

with a lower risk of thrombotic events, including in those who are refractory to other treatments. It may therefore be a drug to consider for patients with an increased thrombotic risk, such as those with coronary artery disease, diabetes, advanced age or obesity. An interesting finding in phase 3 trials was the greater benefit in platelet response and bleeding events when fostamatinib was used as second-line therapy (i.e. after steroids or IVIg) compared to third- or later-line therapy. Notably, the higher the number of previous lines administered, the lesser was the response. However, once achieved, the response was maintained no matter the number of lines of treatment previously received. These findings need to be confirmed in larger clinical studies. Additional work investigating earlier use of fostamatinib and whether this increases efficacy further, or could terminate autoimmune disease early, would also be of interest. In addition, the use of fostamatinib may be preferred over immunosuppressive treatments for ITP in view of the COVID-19 pandemic.

Adult wAIHA is a potentially a life-threatening autoimmune disease, and medical management can be challenging, with no currently approved treatments. The promising results with fostamatinib in the treatment of patients with a history of wAIHA who had relapsed following one or more prior treatments offers some hope in this difficult-to-treat disease. A phase 3 study (NCT03764618) to further investigate the results observed in this study is nearing completion and are awaited with interest [103].

Fostamatinib has also been assessed in other autoimmune diseases (including RA, IgA nephropathy, graft-versus-host disease [GVHD], and wAIHA) and cancer (including B-cell cancers, solid tumors, and *T*-cell lymphomas), as well as in renal transplantation (to prevent GVHD) and, more recently, myelofibrosis with thrombocytopenia, and COVID-19. While encouraging results have been reported for many of these disorders further research is necessary to determine its overall efficacy and clinical benefit.

Since 2013, several other SYK inhibitors have entered clinical trials, including entospletinib, HMPL-523, GSK2646264, lanraplenib, and cevidoplenib. Ongoing clinical studies with SYK inhibitors include phase 1 trials of fostamatinib for ovarian cancer and chronic GVHD, and of HMPL-523 for ITP; phase 2 studies of cevidoplenib for ITP, and of fostamatinib for COVID-19, renal transplantation, and myelofibrosis; phase 3 studies of entospletinib for *NPM1*-mutated AML, and of fostamatinib for COVID-19 and wAIHA; and a phase 4 study of fostamatinib in ITP [79]. The range of indications being studied reflects the mechanism of action of SYK inhibitors, and their ability to affect multiple signaling pathways.

At the current time, the potential for SYK inhibitors to help in the treatment of patients with severe COVID-19 is of particular interest. They have the potential to target multiple aspects of COVID-19 pathogenesis including thrombosis, without affecting normal hemostasis. Data from the first study of fostamatinib in COVID-19 are encouraging; results of three other ongoing studies are awaited with interest.

Combination therapy with fostamatinib has not been studied in a clinical trial. The rationale for combination therapy is to target different mechanistic pathways to achieve better response rates, prevent complications of poorly controlled disease, and minimize drug toxicities. A case series by Hughes et al. provides clinical insight into the use of both fostamatinib and a TPO-RA for ITP during transitional periods of tapering off and/or switching from one therapy to another [104]. Additional clinical data and real-world evidence are needed for both short-term and long-term efficacy and safety of fostamatinib in combination with other therapies to manage ITP.

In the future, it is hoped that the ongoing trials in autoimmune indications other than ITP, as well as in hematological malignancies and other disorders, confirm the promise of SYK inhibitors. The potential for SYK inhibitors such as fostamatinib to be used as part of combination therapy in hematological malignancy and immune-mediated inflammatory disorders may also be an area of interest.

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