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Efficacy and Safety of Janus Kinase Inhibitors in Lupus Nephritis Patients- Clinical Trials and Case Reports

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect multiple organs and systems that has a variable clinical course and prognosis among different patients. Lupus nephritis (LN) is one of the most common and severe organ manifestations of SLE which is associated with significant morbidity and mortality with up to 20% of patients progressing to end stage renal disease. Despite the improvements in therapeutic options, there is a significant proportion of refractory patients and a considerable amount of damage accrual and treatment associated morbidity even among patients that respond to the current treatment modalities. Janus kinase (JAK) inhibitors are currently successfully used in rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis patients. JAK inhibitors simultaneously block the signalling of multiple cytokines and represent a promising class of therapeutic agents for SLE which has a high immunological heterogeneity. Some animal studies demonstrated the significance of JAK/STAT pathway in the pathogenesis of LN and the possible role of JAK inhibitors in alleviating the renal inflammation in animal models of LN. This review covers the clinical data on the use of JAK inhibitors in LN patients by focusing on the clinical trials and few case reports that assess the efficacy and safety of JAK inhibitors in LN patients.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect multiple organs and systems with a highly variable clinical course and prognosis among different patients[1]. This disease has a complex pathogenesis which includes a combination of genetic factors, environmental triggers, hormonal factors and overproduction of various cytokines[2]. Lupus nephritis (LN) is one of the most common and severe organ manifestations of SLE, which is associated with significant morbidity and mortality with up to 20% of patients progressing to end stage renal disease (ESRD)[3]. Glucocorticoids, antimalarials, conventional immunosuppressive agents (azathioprine, mycophenolic acid derivatives, cyclophosphamide, calcineurin inhibitors) have been widely used in LN patients with variable success[4]. With the addition of biologic agents into the therapeutic armamentarium of rheumatologists, agents such as rituximab and belimumab became available for treatment of LN[5]. Despite the improvements in therapeutic options, there is a significant proportion of refractory patients and a considerable amount of damage accrual, treatment associated morbidity and suboptimal health related quality of life even among patients that respond to the current treatment modalities[6]. There is definitely more room for improvement and an unmet need for new therapeutic options.

Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway is responsible for signal transduction of various cytokines (such as interleukin 2, interleukin 6, interleukin 12, interleukin 23, interferon α and β) into the cell. The significance of this pathway in the pathogenesis of various autoimmune diseases is now well recognized[7]. Janus kinase (JAK) inhibitors are currently successfully used in rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis patients[8]. This group of drugs exert multitargeted effects by simultaneously blocking the signalling of multiple cytokines and represent a promising class of therapeutic agents for SLE which has a high immunological heterogeneity[6]. Their oral administration also makes JAK inhibitors a more practical treatment option[9].

A recent randomized, open-label, noninferiority, postauthorization, safety end-point trial involving patients with active rheumatoid arthritis despite methotrexate treatment who were 50 years of age or older and had at least one additional cardiovascular risk factor compared tofacitinib and tumor necrosis factor inhibitors. This study demonstrated higher risks of major adverse cardiovascular events and cancers in tofacitinib patients compared to tumor necrosis factor inhibitors where tofacitinib failed to meet noninferiority criteria[10]. This study raised concerns for the safety of JAK inhibitors.

The study of Wang et al demonstrated that JAK/STAT pathway is implicated in the progression of renal inflammation in MRL/lpr mice and targeting this pathway may provide a potential therapetic strategy for LN[11]. This hypothesis is supported by various animal studies that demonstrated the efficacy of tofacitinib[12,13], baricitinib[14], CEP-33779 (a selective JAK-2 inhibitor)[15] in alleviating renal inflammation in animal models of LN. However not all animal studies report the efficacy of JAK inhibitors. The animal study by Wei et al demonstrated that despite improving plasma autoantibodies, baricitinib did not significantly reduce proteinuria or improve the histological markers of activity and chronicity in MRL/MpJ-Fas^{lpr} model of lupus nephritis[16].

These preclinical studies raised the interest of clinicians in performing clinical trials that assess the efficacy of JAK inhibitors in the treatment SLE, including LN. They also paved the way for off-label case based uses of JAK inhibitors in LN patients in real world setting. This review covers the limited clinical data on the use of JAK inhibitors in LN patients by focusing on the clinical trials and few case reports that assess the efficacy and safety of JAK inhibitors in LN patients.

Clinical Trials

Clinical trials that explore the efficacy and safety of JAK inhibitors in LN are listed in Table 1.

Table 1: Clinical trials that explore the efficacy and safety of JAK inhibitors in patients with lupus nephritis

Name of the Trial	Name of the Investigated JAK Inhibitor	Status of the Trial
NCT03285711	Filgotinib	Completed
NCT03943147	Deucravacitinib	Terminated
NCT05432531	Baricitinib	Ongoing

Filgotinib (NCT03285711- Completed)

Filgotinib is a potent JAK inhibitor, with preferential selectivity for JAK1 and lanraplenib (previously known as GS-9876) is a selective and potent ATP-competitive inhibitor of spleen tyrosine kinase (SYK)[17].

STUDY PROTOCOL:

A multicenter, randomised, double-blind trial was performed from September 2017 to February 2020 at 15 centres in the USA. This trial investigated the efficacy and safety of filgotinib and lanraplenib in in LN patients that had histopathologically confirmed (biopsy performed within 18 months prior to screening) Class V LN (with or without accompanying Class II LN), with a urine protein excretion ≥ 1.5 g/day and an estimated glomerular filtration rate ($eGFR_{MDRD}$ ≥ 60 mg/min/1.73m^2 based on the Modification of Diet in Renal Disease (MDRD) formulation. Membranous lupus nephritis was treated with at least one immunosuppressive therapy (mycophenolate mofetil, azathioprine, tacrolimus, cyclosporine, cyclophosphamide or chlroambucil) for at least 6 consecutive months within 1 year before screening. Oral glucocorticoids were allowed at doses that were ≤20 mg/ day of prednisone or equivalent and remained stable through week 16 of the study. Patients were also permitted to continue hydroxychloroquine at a stable dose. Treatment with an ACE inhibitor or angiotensin II receptor blocker, or documented intolerance to these agents was required. Patients were excluded if they had received previous treatment with a JAK inhibitor within 3 months of day 1 or rituximab or other B cell depleting agent within 6 months of day 1[17].

In order to increase recruitment in March 2018, the protocol was changed: Window for kidney biopsy was extended to 36 months prior to screening, eGFR criteria was changed to include patients with eGFR≥ 40 mg/min/1.73m^2, the duration of prior immunosuppressive treatment was changed to the discretion of investigator and additional treatments such as methotrexate, leflunomide and moderate-dose to high-dose glucocorticoids were allowed[17].

Patients were randomised in a 1:1 ratio to 200 mg filgotinib or 30 mg lanraplenib. Randomisation was stratified by prior cyclophosphamide treatment. Patients who had ≥35% reduction in proteinuria at 16 weeks continued to receive their assigned blinded study treatment for 16 more weeks. For patients who did not have a ≥35% reduction in proteinuria, their study treatment was switched for the next 16 weeks in a blinded fashion. After 32 weeks of blinded treatment, patients who had a ≥35% reduction in urinary protein excretion from day 1 or from week 16 continued their assigned blinded treatment for 20 more weeks in the Extended Blinded Treatment Phase. Subjects who did not achieve a ≥35% reduction in urinary protein excretion at week 32 compared with baseline were allowed to continue whichever study treatment led to the greatest reduction in proteinuria at the subject's and investigator's discretion. The use of a new, or increased dose of an existing, immunosuppressant agent, including glucocorticoids required discontinuation of the study treatment[17].

A total of nine patients were recruited who were randomised to receive filgotinib (n=5) or lanraplenib (n=4). Three subjects completed the study, 6 patients discontinued the study (3 due to adverse effects, 2

due to lack of efficacy and one due to violation of protocol)[17].

EFFICACY:

At week 16, the median percent change from baseline in 24 hour urine protein was −50.7% for the filgotinib group (n=4) and −2.8% for the lanraplenib group (n=1). At week 16, one of the patients in the filgotinib arm changed to lanraplenib, due to a 12% reduction in proteinuria. This patient continued on lanraplenib for the remainder of the study, with a 94.6% reduction in 24- hour proteinuria at week 52 compared with baseline. Two patients in the filgotinib group remained on filgotinib for the duration of the study, with a median reduction in 24- hour urine protein of 78.3% at week 52. Systemic lupus eythematosus disease activity index from the Safety of Estrogens in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA- SLEDAI) total score remained stable for three of the four patients in the filgotinib group from baseline to week 16. No improvement in anti-dsDNA or complement levels was observed in either group[17].

SAFETY:

Majority of patients in both treatment periods reported at least one adverse event (AE). The most common adverse events during the study were neutropenia and bronchitis (two patients each). Up to week 16, grade ≥3 adverse events were reported in one subject (20%) in the filgotinib group and in three subjects (75%) in the lanraplenib group. After week 16, only one subject reported an AE of grade ≥3 (filgotinib to lanraplenib group). Most adverse events were not considered related to the study drug. One subject in the lanraplenib arm reported two treatment-emergent serious adverse events (SAEs) and both were not considered to be related to study drug. The following grade ≥3 treatment emergent AEs (TEAEs) were reported: neutropenia, lymphopenia, hypercholesterolemia, hypoalbuminemia, worsening of SLE and acute kidney injury (one subject each). From baseline to week 16, one subject (20%) in the filgotinib group and two subjects (50%) in the lanraplenib group prematurely discontinued study drug due to TEAEs. No TEAE causing study drug discontinuation was reported after week 16. There were no reports of venous thromboembolism, herpes zoster, malignancy or death during the study[17].

Although the number of patients included were very limited, this study may support future studies using filgotinib or other JAK inhibitors in (especially Class V) LN patients[6,17].

Deucravacitinib (NCT03943147- Terminated)

Deucravacitinib is an allosteric TYK2 inhibitor with a high specificity to TYK2 pseudokinase domain. TYK2 is a member of JAK family but TYK2 inhibitors have a different profile than that of other JAK inhibitors. Receptors of cytokines such as interleukin-12, interleukin-23 and type I interferons are TYK-2 dependent, which differ from JAK-1 or JAK-3 dependent cytokine receptors (such as interleukin-2, interleukin-15 and interleukin-6 receptors) or JAK-2 dependent receptors (such as the receptors of erythropoietin, thrombopoietin and granulocyte-macrophage colony stimulating factor)[6].

NCT03943147 was a phase 2, randomized, double-blinded, placebo controlled clinical trial aimed to evaluate the safety and effectiveness of BMS-986165 (deucravacitinib) with background treatment in participants with LN. This study was terminated due to insufficient enrollment. Inclusion criteria were 18-75 year old patients that meet Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) criteria for SLE, that have renal biopsy compatible with International Society of Nephrology/ Renal Pathology Society (ISN/RPS) Class III, Class IV (segmental or global) LN with or without Class V LN and that have a urine protein:creatinine ratio (UPCR) ≥1.5 mg/mg or UPCR ≥1 mg/mg assessed with a 24-hour urine specimen. Exclusion criteria were pure Class V LN or screening estimated glomerular filtration rate ≤30 mL/min/1.73 m^2 or dialysis within 12 months before screening or plans for dialysis

within 6 months after enrollment in the study or presence of end-stage renal disease[18].

In part A, all study participants would receive mycophenolate mofetil (MMF) at a dose of 1.5 to 3.0 g/day for 12 weeks. Participants who meet the criteria to continue in Part B but do not meet the randomization criteria could continue on open-label MMF with or without corticosteroids. In Part B, participants with an inadequate renal response to MMF would be randomized to blinded study treatment deucravacitinib 3 mg BID, deucravacitinib 6 mg BID, or placebo BID, as add-on therapy to MMF. No participants were randomized to receive deucravacitinib 3 mg BID or placebo BID due to low enrollment. This study was terminated due to insufficient enrollment, only 16 patients were enrolled. Six patients completed part A and 10 patients did not complete part A (4 due to other reasons, 1 due to adverse event, 1 due to non-compliance with study drug, 1 due to protocol specified withdrawal criterion being met and 3 due to termination of the study by sponsor). A total of 6 patients started Part B. Three patients completed Part B wheras the remaining 3 were unable to complete the study due to sponsor terminating the study. Only one patient received deucravacitinib in Part B. UPCR decreased 34.9 percent in week 24 in that patient. That patient failed to achieve partial renal response (≥ 50% reduction from baseline in 24-hour UPCR) and complete renal response (UPCR ≤ 0.5 mg/mg and an estimated glomerular filtration rate ≥ 60 mL/min or ≤ 20% decrease from baseline.) in 24 weeks or 52 weeks[18].

Among the sixteen patients that participated in Part A, 1 patient had serious adverse event (COVID-19 pneumonia) and 7 patients had other adverse events (1 patient had sensorineural deafness, 1 patient had abdominal discomfort, 1 patient had abdominal distension and 1 patient had hematochezia, 1 patient had pyrexia, 1 patient had gallbladder polyp, 1 patient had nasopharyngitis, 1 patient had upper respiratory tract infection, 1 patient had urinary tract infection, 1 patient had blood pressure increase, 1 patient had weight increase, 1 patient had arthralgia, 1 patient had muscle spasms and 1 patient had dizziness. The only patient that completed Part B had COVID-19 as a serious adverse event. As other adverse events, he had flank pain, prolonged prothrombin time, prolonged activated partial thromboplastin time increased international normalized ratio[18]. Most adverse effects do not seem to be related to the study drug.

Baricitinib (NCT05432531-Ongoing)

A phase 3 trial of selective JAK1 and JAK2 inhibitor baricitinib in patients with lupus nephritis is currently ongoing [NCT05432531]. Eligibility criteria include 18-60 years old LN patients. Patients with a history of cardiac disease and thrombosis will be excluded. Patients will be randomized to receive monthly IV cyclophosphamide (0.7 g/m^2/month) or baricitinib (4 mg/day po). Primary outcome measure will be the quantity of protein in 24 hour urine. Secondary outcomes will be serum complement 3 level, serum anti dsDNA titers and SLEDAI-2K at the third and sixth months[19].

Case Reports

Case reports that describe the use of JAK inhibitors are listed in Table 2.

Table 2: Case reports that describe the use of JAK inhibitors in patients with lupus nephritis

Authors, Year	Name of the JAK inhibitor	Patient Characteristics
Garufi et al, 2020	Baricitinib	A rhupus patient with class V lupus nephritis
Peng et al, 2023	Baricitinib	A class IV+V lupus nephritis patient with a novel DExD/H-box helicase 58 (DDX58) mutation that causes increased interferon signature

Garufi et al report the successful use of JAK inhibitors in 2 rhupus patients (19). One of these patients is a 52 year old Caucausian male patient diagnosed with Class V LN who later developed symmetric polyarthritis, anti cyclic citrullinated peptide antibodies and rheumatoid factor positivity. He previously received glucocorticoids, methotrexate, azathioprine, mycophenolate mofetil, cyclosporine A, cyclophosphamide, rituximab. Abatacept temporarily controlled renal disease and the articular flares during the following years. Then tacrolimus was added to abatacept for a renal flare. Since arthritis and residual proteinuria persisted, abatacept was stopped and baricitinib 4 mg/day was added to tacrolimus and hydroxychloroquine. After 6 months the patient achieved a stable improvement in the joint involvement and complete renal remission with a reduction of proteinuria from 750 mg/day to 230 mg/day in 6th month[20].

Peng et al identified a novel DExD/H-box helicase 58 (DDX58) pathogenic variant R109C in 5 untreated families with lupus nephritis. This variant is a gain of function mutation, elevating type I interferon signaling due to reduced autoinhibition which leads to retinoic acid inducible gene I (RIG-I) hyperactivation, increased RIG-I K63 ubiquitination and mitochondrial antiviral-signaling protein (MAVS) aggregation. Transcriptome analysis revealed an increased interferon signature in patients' monocytes. One of these patients was diagnosed with class IV+V LN when she was 12 years old. She received intravenous methylprednisolone and cyclophosphamide for induction therapy, which was followed by a maintenance regimen of oral glucocorticoids and azathioprine. When she was 28 years old, her disease relapsed and she was given intravenous glucocorticoid and cyclophosphamide. After a partial remission with this reinduction regimen, she received a maintenance regimen of methylprednisolone, MMF and hydroxychloroquine for 6 years. Despite this treatment her titer of autoantibodies remained high and complement levels were low. Mycophenolate mofetil was stopped for 5 weeks and then she received oral baricitinib for 6 months. Baricitinib enabled decrease of antinuclear antibody titer, elevated complement levels and stabilized disease activity. Renal disorder was not alleviated (no details concerning the serum creatinine level or proteinuria were provided in the text). No adverse effects or serious adverse events were present. Baricitinib effectively suppressed proinflammatory cytokines and expression of interferon stimulated genes in especially in CD14 positive peripheral blood monouclear cells. The authors claimed that suppression of type 1 interferon signature in this patient with baricitinib provided clinical implication that JAK inhibitors may be a potential treatment strategy in LN patients with DDX58 R109C variant[21].

Conclusion

Heterogeneity of organ involvement and the highly variable clinical course of SLE makes designing clinival trials in SLE challenging[22]. There are many clinical trials that aim to assess the efficacy and safety of JAK inhibitors in SLE[1,2,6]. However very few studies so far have focused on the efficacy and safety of JAK inhibitors in LN.

Unfortunately, very few Class 5 LN patients joined filgotinib trial and deucravacitinib trial was terminated due to insufficient enrollment[17,18]. In filgotinib study, 4 patients on this drug achieved a reduction in median proteinuria of 50.7 percent compared to baseline. SELENA-SLEDAI score stablized in 3 of these 4 patients at week 16. Two patients remained on filgotinib for 52 weeks and they achieved a median reduction in 24-hour urine protein of 78.3% at week 52[17]. Only 1 deucravacitinib patient completed part B and that patient failed to achieve partial renal response[18]. The case report of the rhupus patient with Class V LN and residual proteinuria described significant reduction in proteinuria when baricitinib was added to tacrolimus and hydroxychloroquine[20]. In the other case report, baricitinib helped reduction of ANA titer and increased complement levels but renal disorder was not alleviated. The authors did not state the proteinuria levels before and after baricitinib treatment[21]. When the issue of safety is concerned, no patients had major adverse

cardiovascular events, venous thromboembolism, herpes zoster, malignancy or death[17,18,20,21]. Patients that received filgotinib had neutropenia, leukopenia, hypercholesterolemia as the treatment emergent adverse events[17]. However, none of the studies or case reports can address the long term safety concerns that make use of JAK inhibitors risky in real life setting.

In conclusion, the amount of data coming from clinical trials and case reports on the use of JAK inhibitors in LN is very limited and comes mostly from Class V LN patients. With this current limited data, JAK inhibitors (filgotinib and maybe baricitinib) can be beneficial in reducing proteinuria in Class V LN patients. However the very limited number of LN patients that received JAK inhibitors and the relatively short duration of these treatments should be kept in mind before conclusions can be drawn about the efficacy and long term safety of these drugs in LN patients. Future studies with larger number of patients and longer follow up durations are needed in order to have a better understanding of the efficacy and safety of JAK inhibitors in patients with lupus nephritis.

Conflict of Interest:

None

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None

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