Review

Can inhibitors of JAK1 be used as an effective treatment for type 1 diabetes?

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Abstract

HLA-I hyperexpression on β-cells is a key feature of type 1 diabetes mellitus (T1DM) and increases visibility towards cytotoxic T cells. Modulating HLA-I expression by disrupting the JAK/STAT signalling pathway has been proposed as an attractive target. JAK1 is particularly interesting for its role as a signal transducer in multiple IFN induced pathways. This review will evaluate whether inhibitors of JAK1 could be used as an effective treatment for T1DM. Preclinical evidence suggests that JAK1 inhibitors can decrease the hallmarks of T1DM. Clinical evidence also indicates improved glycaemic control and decreased exogenous insulin requirements in T1DM patients. JAK1 inhibitors may also reduce biomarkers of diabetic kidney disease, thus widening the therapeutic window of treatment in patients. JAK1/2 inhibitors like Baricitinib have already been used clinically in the treatment of rheumatoid arthritis safely. However, individuals with T1DM are at increased risk of adverse effects. The duration of treatment in T1DM is likely significantly longer than other autoimmune conditions and may lead to severe anaemia. Thus, longitudinal studies are required to identify the long-term safety of JAK1 inhibitors. The ongoing JAKPOT trial investigating a JAK1 specific inhibitor could provide more evidence on the future of T1DM management.

Abbreviations

DKD – diabetic kidney disease
ER – endoplasmic reticular
HLA-1 – human leukocyte antigen-1
NOD – non-obese diabetic
T1DM – type 1 diabetes mellitus

Introduction

Type 1 diabetes

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterised by the infiltration of CD8+ T cells among other immune cells into the pancreatic islets of Langerhans.[1] These immune cells selectively target insulin-secreting β-cells which results in in loss of β-cell mass and function. Consequently, individuals with T1DM have decreased endogenous insulin production and suffer from impaired glucose homeostasis. These individuals are therefore required to monitor their blood sugar and administer daily exogenous insulin injections to manage their blood glucose levels. Nevertheless, individuals may still experience inadequate glycaemic regulation and are at risk of nephropathy, neuropathy and cardiovascular complications.[1] It has also been reported that 38% of people with T1DM have experienced severe hypoglycaemia due to hypoglycaemic unawareness, which may cause seizures and brain damage.[2]

T1DM is a condition of growing concern. It is estimated that 8.4 million people are currently living with T1DM globally. However, this figure is expected to rise to 13.5-17.4 million by 2040.[1,3] As such, novel

treatment strategies that modify disease state rather than manage the disease may be an attractive solution to the rising economic and public health burden of T1DM. Furthermore, these alternative therapeutics could potentially address the limitations of current T1DM treatments.

JAK/STAT signalling

Interestingly, increased expression of the immune recognition complex human leukocyte antigen I (HLA-I) has been identified on the surface of β-cells in T1DM patients but not in people without diabetes.[1,4] This has led researchers to investigate whether therapeutics could slow down T1DM development by preventing β-cell death via immunomodulation.

It has been suggested that HLA-1 hyperexpression in T1DM is driven via type I, II, III interferon signalling following viral infection via the JAK/STAT pathway. Although JAKs are a family of tyrosine kinases (JAK1, JAK2, JAK3, TYK2), JAK1 is a common denominator in the signal transduction of all three of these interferons.[5,6] As such, inhibitors of JAK1 could prevent downstream signalling via multiple pathways (**Figure 1**). Therefore, the aim of this review is to evaluate if inhibitors of JAK1 could be used as an effective treatment in T1DM. It will also explore the safety profile of these drugs.

Method

PubMed and TRIP databases were used to identify the literature for this review. Searching for the terms ((Type 1 Diabetes) AND ((JAK inhibitor) OR (JAK1 inhibitor)) generated 334 papers (**Figure 2**). Eligibility of these papers was assessed by screening the title and abstract for relevancy. Inclusion criteria were articles that focused on T1DM and inhibitors of JAK1. Exclusion criteria were incomplete articles and papers published before 2010 due to the novelty of this research. This resulted in 14 papers being used for discussion.

Discussion

Preclinical effects on β-cell function

Inhibitors of JAK1 have been used on T1DM models with positive results.[5-10] Despite the differences in T1DM models amongst the studies, these inhibitors were found to significantly decrease hallmarks of T1DM, namely, HLA-I hyperexpression, insulitis, and endoplasmic reticular (ER) stress (**Table 1**). However, these studies found that HLA-I is re-upregulated after ceasing treatment. This implies that individuals will need persistent exposure to inhibitors of JAK1 for the treatment to be effective.

Ge et al found that LN3103801 was able to decrease IFN- γ induced HLA-I hyperexpression and prevent diabetes in non-obese diabetic (NOD) mice before and after administering anti-PD-L1.[8] The same results were also seen after hyperglycaemia onset, suggesting JAK1 inhibitors could be used after T1DM onset. Although, a study found that EndoC-βH1 cells treated with Baricitinib after being exposed to IFN- α did not affect HLA-I hyperexpression.[9] This is significant as JAK inhibitors prevent β-cell death by disrupting immune cell interaction. However, symptoms of T1DM typically presents after a critical mass of β-cells have been destroyed.[1] Therefore, it is important to identify the window in which these drugs prevent targeted β-cell destruction. Notably, Ge et al induced diabetes via anti-PD-L1 which is not typical of T1DM pathogenesis and may explain the different results. However, these studies used different model organisms, dosages and JAK1/2 inhibitors, which limits comparability.

Importantly, inhibitors of JAK1 seemed more effective than other classes of JAK inhibitors such as TYK2. Dos Santos et al identified that Baricitinib and Ruxolitinib (both JAK1/2 inhibitors) were less potent inhibitors of HLA-1 upregulation than TYK2 inhibitors.[10] Despite this, JAK1/2 inhibitors were able to inhibit ER stress markers unlike TYK2 inhibitors. This indicates that JAK1/2 inhibitors could work two-fold by preventing both targeted β-cell destruction and dysfunction. However, the clinical implications of this have not been investigated. Clinical effects on β-cell function

JAK1 specific inhibitors have yet to be investigated in humans with T1DM. However, the use of JAK1/2 inhibitors in a STAT1 gain of function case study has served as foundational evidence for its clinical use.[11] A 15-year-old boy with T1DM was given Ruxolitinib after presenting with chronic mucocutaneous candidiasis. Twelve months after starting Ruxolitinib treatment, the individual discontinued exogenous insulin therapy and was normoglycemic until the end of the study 12 months later. More interestingly, the patient was given Ruxolitinib 9 months after being diagnosed with T1DM, well past the "honeymoon period" in which β-cell function can be temporarily restored. Follow up of this individual could be beneficial in determining whether these effects are long lasting. This study is supported by another case report whereby Baricitinib improved glycaemic control in a 71-year-old patient with slowly progressive T1DM.[12] Shortly after beginning Baricitinib therapy, the individual's daily exogenous insulin requirements decreased by 35% and this was maintained for the duration of the 52-week trial. These studies suggest the possibility that T1DM can be improved and perhaps even reversed in humans. However, these studies are limited by their small sample size (n=1) and their atypical T1DM profiles.

Recently, the BANDIT trial, a phase 2, double blind, randomised controlled trial (n=91) explored whether Baricitinib could preserve β-cell function and improve metabolic markers compared to placebo.[13] Mean c-peptide levels were used to measure β-cell function. Patients (10-30 years old) who had been recently diagnosed (<100 days) with T1DM were orally administered Baricitinib daily for 48 weeks. Patients taking Baricitinib showed sustained levels of c-peptide, indicating maintained insulin secretion for the duration of the trial. Additionally, individuals required 21% less exogenous insulin on average. However, several limitations were identified. The sample population consisted primarily of white individuals (88%) older than 10 years without any pre-existing conditions such as cytopenia or history of thrombosis. Therefore, this study cannot be generalised to other demographics. Given the juvenile onset of T1DM, a cohort with younger individuals could also better reflect the intended target population and provide insight into the efficacy of Baricitinib. Additionally, the relatively short trial (48 weeks) did not determine the long-term effects of this treatment. Seeing as T1DM is a chronic condition, long-term follow up could reveal the sustained effects of this intervention.

Treating diabetic complications

The immunomodulatory and anti-inflammatory effects of JAK inhibitors have also been investigated in the treatment of diabetic complications.[14-16] This could potentially widen the therapeutic window for individuals who no longer have sufficient functional β-cell reserves. Two studies investigating whether Baricitinib could modulate markers of diabetic kidney disease (DKD) found similar results. After 24 weeks, a phase 2 randomised control trial (n=129) found that Baricitinib significantly reduced inflammatory cytokine levels in the blood and urine. Compared to placebo, they also identified a 40% decrease in albumin to creatine ratio in urine, a gold standard in measuring DKD.[14] Similarly, Curovic et al (n=26) identified decreased urinary albumin-creatine ratio when Baricitinib was taken in rotation with three other non-JAK inhibiting drugs.[15] However, this study found that Baricitinib only worked in 13% of individuals and was the least effective of the four drugs at lowering urinary albumin to creatinine ratio. Interestingly, patients with T1DM responded best to Baricitinib compared to type 2 diabetes.[15] This suggests that individualisation of treatment could have potential in T1DM patients. However, the study is limited by the small sample size and short treatment duration of only 4 weeks. Baricitinib was also investigated to treat cardiovascular neuropathy in humans.[16] However, this study did not identify any significant results. Although, this study did not contain a control group and was at risk of a carry-over effect from a

previous crossover trial.

Safety profile

The safety profile of JAK1/2 inhibitors in T1DM management is mixed. Baricitinib, a JAK1/2 inhibitor has been safely used in humans as a treatment for rheumatoid arthritis and atopic dermatitis.[17] However, this study identified that individuals with rheumatoid arthritis and diabetes mellitus compared to individuals with just rheumatoid arthritis were at significantly higher risk of major adverse cardiovascular events, venous thromboembolism, serious infection and mortality. Therefore, patient disease status and response to treatment should be considered when treating patients with Baricitinib. Tuttle et al (n=129) also identified anaemia in 32% of T1DM patients taking Baricitinib compared to 3.7% of patients in the control group.[14] Interestingly, the BANDIT trial did not identify a higher risk of adverse drug reactions compared to placebo.[13] However, this may be due to the small sample size and short duration of the trial. Additionally, the study excluded individuals with anaemia and thrombosis who may be at higher risk of adverse events.

Although JAK inhibitors seem surprisingly well tolerated for drugs that disrupt important pathways involved in processes such as immunity,[14] longer duration of treatment may lead to more severe anaemia or infection. It is important to consider that the duration of drug persistence in treating either T1DM or DKD would likely be greater than the duration of these studies. Therefore, longitudinal trials could be done to assess the long-term safety and efficacy of Baricitinib in managing T1DM clinically. Interestingly, erythropoietin signals through JAK2 dependent pathways.14 Therefore, the risk of anaemia and additional off-target effects could potentially be reduced by using a selective JAK1 inhibitor. The JAKPOT trial will in part investigate Abrocitinib, a specific JAK1 inhibitor in recently diagnosed T1DM patients.[18] However, this study faces many of the same limitations in identifying adverse drug reactions as the BANDIT trial, such as small sample size (n=78). Additionally, it is unclear whether individuals with co-existing conditions are eligible for the trial.

Conclusion

Inhibitors of JAK1 as an adjuvant in treating T1DM is promising. However, the lack of young patients in clinical trials means that results cannot be generalised to a significant proportion of individuals with T1DM. Furthermore, the lack of standardisation among studies using JAK inhibitors makes it difficult to determine if there is an optimal delivery route, dosage, or type of JAK1 inhibitor in T1DM treatment. Future studies should investigate the long-term effects and safety of JAK1 specific inhibitors in T1DM treatment.

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Lucas Gadaleta

Hi, I am Lucas, a second-year medical student at the University of Exeter. This article was written as part of a student selected component which enabled me to develop my interest in endocrinology. Notably, this experience enabled me to participate in research that is trying to better understand and characterise type 1 diabetes aetiology. My other passion lies in following a career in orthopaedics, a unique specialty where you can deliver both life improving care and play with power tools.

Table 1. Inhibitors of JAK1

Inhibitor	Outcome	Model	Study
AZD 1489 (JAK1/2 inhibitor)	- Decreased HLA-1 upregulation - Decreased insulitis - Prevented development of T1D Reversed diabetes in newly diagnosed NOD mice	NOD mice Human islets	Trivedi et al[7]
ABT 317 (JAK1 selective inhibitor)	- Decreased HLA-1 upregulation - Decreased insulitis - Reversed diabetes in newly diagnosed NOD mice	NOD mice	Ge et al[6]
LN3103801 (JAK1/2 inhibitor)	- Decreased HLA-1 upregulation - Decreased insulitis - Prevented anti-PD-L1 induced diabetes	NOD mice	Ge et al[8]
Ruxolitinib (JAK1/2 inhibitor)	- Decreased HLA-I upregulation - Decreased ER stress markers	EndoC-βH1 β-cells	Coomans de brachene et al[9]
Baricitinib (JAK1/2 inhibitor)	- Decreased HLA-I upregulation - Decreased ER stress markers - Prevented beta cell apoptosis	EndoC-βH1 β-cells Human islets	Colli et al[5]
Baricitinib & *Ruxolitinib*	- Decreased HLA-I upregulation - Decreased ER stress markers	EndoC-βH1 β-cells	Dos Santos et al[10]

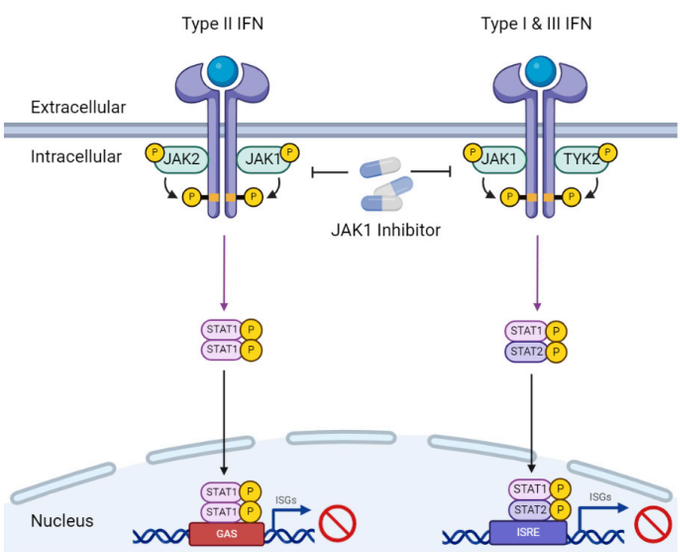

Figure 1. JAK1 inhibitor mechanism of action. Type II IFN signals via JAK1/JAK2 whereas type I & III signal via JAK1/JAKIII. JAK1 inhibitors target a common element to both signalling pathways to modulate downstream signalling. This results in decreased expression of interferon stimulated genes (ISGs). JAK (Janus kinase); STAT (Signal transducers and activators of transcription); GAS(Gamma interferon activation site); ISRE (Interferon stimulated response element). Adapted from Russell, Richardson, Morgan (2023),[4] with thanks, using Biorender.

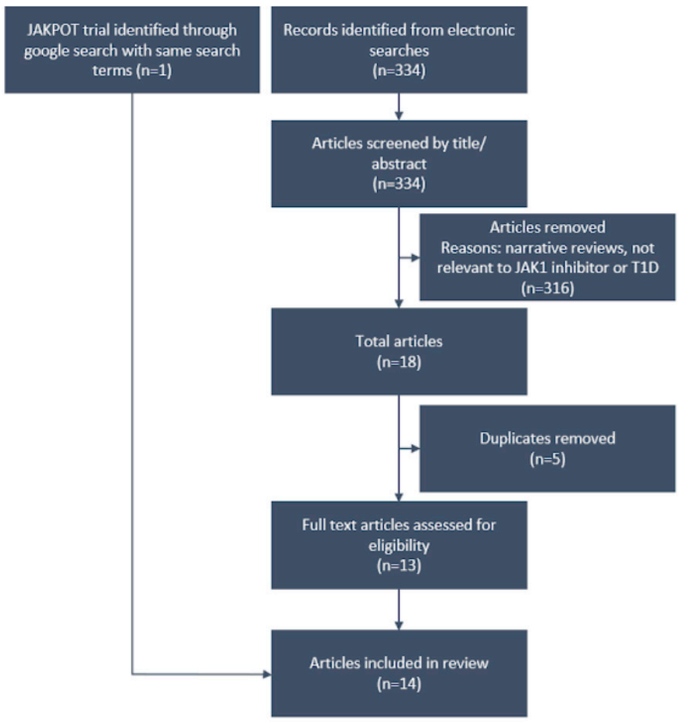

Figure 2. PRISMA diagram. Workflow for literature search and selection.