CASE REPORT

GSK2586184, a JAK1 selective inhibitor, in two patients with ulcerative colitis

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SUMMARY

Tofacitinib, a non-selective Janus kinase (JAK) inhibitor, is effective in inducing clinical and endoscopic remission in patients with active ulcerative colitis (UC). Tofacitinib inhibits cytokine signalling through blockade of JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). Adverse events including neutropenia and anaemia resulting from JAK2 inhibition have been observed in actively treated patients. By selectively targeting JAK1, such adverse events could be expected to be avoided. This open label study was designed to enrol 15 patients with UC, however the trial was discontinued after two inclusions due to safety concerns with the agent in a parallel trial for systemic lupus erythematosus. GSK2586184 was administered in two patients with moderate-to-severe UC. The JAK1 selective inhibitor GSK2586184 was well tolerated and induced clinical and endoscopic response in two patients with moderate-to-severe UC. In addition, treatment with GSK2586184 decreased histology scores and faecal calprotectin levels at early withdrawal.

BACKGROUND

Ulcerative colitis (UC) is the most common inflammatory bowel disease worldwide. The disease pattern of UC is characterised by episodes of active disease alternating with remission. In UC, inflammation is limited to the mucosal lining, often localised in the rectum and inflammation may extend more proximally over time. Patients suffer from symptoms such as diarrhoea, rectal bleeding, fatigue and abdominal pain.¹ With the introduction of antibodies against tumour necrosis factor alpha, integrins (vedolizumab) and interleukin (IL) 12/IL23 (ustekinumab), therapeutic options have expanded. However, there is still a need for additional treatments, as loss of response and the need for surgery remains high.²

Tofacitinib ('XELJANZ', Pfizer, New York, USA) is an oral small molecule that blocks activation of cytoplasmic Janus kinases (JAKs) and signalling of cytokines involved in the perpetuation of colitis.³ In two recent phase III UC studies, tofacitinib induced clinical response and remission and, more importantly, mucosal healing after 8 weeks of treatment.⁴ Tofacitinib targets all JAK family members (JAK1, JAK2, JAK3 and TYK2) leading to a profound immune suppression. Serious infections were reported in these studies, including herpes zoster, pneumonia or abscesses. In addition, neutropenia and anaemia have been observed in patients using tofacitinib, which is attributed to inhibition of erythropoietin signalling via JAK2.⁵ Therefore,

selectively targeting one JAK family member could have a therapeutic potential, with a reduction in the risk of adverse events.

The current study was designed as an open label, experimental study to investigate the safety and tolerability of GSK2586184, a JAK1 selective inhibitor, in patients with moderate-to-severely active UC. GSK2586184 was investigated in a development programme for psoriasis, systemic lupus erythematosus (SLE) and UC. Unfortunately, six cases of elevated liver enzymes were observed in patients with SLE during treatment, leading to early discontinuation of the development programme.⁶

This case report demonstrates the potential of GSK2586184, the first JAK1 selective inhibitor investigated in two patients with UC, to improve clinical and endoscopic parameters of disease as well as colonic histopathology. The trial was funded by GlaxoSmithKline and registered on <http://clinicaltrials.gov> as NCT02000453 (GSK protocol 200208).

CASE PRESENTATION

At the time of cessation of this study, GSK2586184 400 mg twice daily was administered to two patients. The first patient was a 48-year-old Caucasian male with moderate left-sided colitis, therapy refractory to aminosaliculates and tacrolimus, not using any concomitant medication at the time of inclusion. At inclusion, he had one to two stools per day more than normal, with faecal blood loss most of the time. The second patient was a 34-year-old male of African-American heritage with severe left-sided colitis, despite the use of 2 g of aminosaliculates at stable dose at the time of inclusion. He had five or more stools per day more than normal, with obvious faecal blood loss. The first patient was treated with GSK2586184 for 7 weeks and the second patient was treated for 2 weeks.

INVESTIGATIONS

No concerns regarding safety and tolerability of treatment with GSK2586184 were reported in either patient. During treatment, each patient reported one adverse event, namely, nasopharyngitis and headache. Both adverse events resolved after 6 and 1 days, respectively, and were assessed as unrelated to the study drug. We observed no abnormalities of potential clinical relevance in clinical chemistry, urinalysis, vital signs or ECG measurements. A minor decrease in lymphocyte counts in both patients was measured, from $1.53 \times 10^9/L$ at baseline to $1.18 \times 10^9/L$ at early withdrawal in the first patient and from $1.26 \times 10^9/L$ to $1.21 \times 10^9/L$

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Figure 1 (A) The Total Mayo score, ranging from 0 to 12 points, decreased in both patients after treatment with GSK2586184 (B) The Mayo individual sub-scores, stool frequency (0–4), rectal bleeding (0–4), physician's global assessment (0–4) and the Mayo endoscopic sub-score (0–3) decreased in both patients after treatment with GSK2586184. (C) The (UCEIS) (0–11) decreased in both patients after treatment. (D) Endoscopy images of patients 1 and 2, treated with decreased in both patients after treatment with GSK2586184 for 7 and 2 weeks, respectively. (E) Serum concentrations of GSK2586184 measured in patient 1 at baseline, at day 14 pre- and post-dose and at day 28 post-dose. UCEIS, Ulcerative Colitis Index of Severity.

in the second patient. In particular, no elevated serum levels of liver enzymes, creatinine or cholesterol were detected during their participation.

OUTCOME AND FOLLOW-UP

The disease severity was assessed using the Total Mayo score, consisting of the following items: stool frequency, rectal bleeding, the physician's global assessment and the Mayo endoscopic sub-score, all ranging from 0 to 3. The Total Mayo score decreased in both patients (patient 1: 7–3; patient 2: 11–3), with no individual sub-score exceeding one point at early withdrawal sigmoidoscopy (figure 1A,B). The Mayo endoscopic sub-score was reduced in both patients (patient 1: 2–1; patient 2: 3–1, figure 1B,D) at early withdrawal endoscopy. In addition, a change from baseline of mucosal appearance was observed as

determined by the Ulcerative Colitis Index of Severity (UCEIS, figure 1C).⁷ GSK2586184 serum concentrations of the first patient, which were collected at different time points before or after the drug was dosed, indicated effective delivery of the drug (figure 1E). Symptomatic clinical remission was partially achieved; the stool frequency score remained one at early withdrawal in the first patient and decreased from 2 to 1 in the second patient. The rectal bleeding score was 0 in both patients at early withdrawal. Clinical response (decrease in Total Mayo ≥ 3 , with decrease rectal bleeding score ≥ 1 or rectal bleeding score 0) and mucosal healing (Mayo endoscopic sub-score ≤ 1 with change from baseline UCEIS) were achieved in both patients at early withdrawal.

Faecal calprotectin and serum C-Reactive Protein (CRP) were measured as biomarkers for disease. Faecal calprotectin

Figure 2 (A) Faecal calprotectin levels decreased in both patients after treatment with GSK2586184. (B) Serum CRP primarily decreased in patient 2 after treatment with GSK2586184. In patient 1, CRP concentrations were low at baseline, the increase was caused by a nasopharyngitis. (C) The Geboes score, ranging from 0 to 5, decreased in biopsies both patients after treatment with GSK2586184. (D) IBDQ scores, ranging from 32 to 224 points, improved after treatment with GSK2586184.

levels decreased from 485 and 1006 µg/g at baseline to, respectively, 120 and 172 µg/g at early withdrawal (figure 2A). Serum CRP levels were low at baseline in the first patient, at week 4 an increase was observed which occurred simultaneously with complaints of nasopharyngitis. In the second patient, serum CRP levels decreased from 7 mg/L at baseline to 4.8 mg/L at early withdrawal (figure 2B). Histologically, both patients also improved, with Geboes scores⁸ decreasing from 1.1 and 3.2 points at screening to 0.2 and 1.2 points, respectively, at early withdrawal (figure 2C). Inflammatory Bowel Disease Questionnaire (IBDQ) scores improved,⁹ from 147 and 160 points at baseline to 170 and 208 points at early withdrawal (figure 2D).

DISCUSSION

In rheumatoid arthritis and inflammatory bowel disease, patients treated with tofacitinib, a pan-JAK inhibitor, adverse events including an increased risk of (opportunistic) infections, a mild increase in serum creatinine levels, increased serum cholesterol levels and suppression of haematological parameters have been reported.^{4 10-12} The study described here was discontinued at an early stage, due to reports of serious adverse events in patients with SLE after administration of GSK2586184. Within the time frame described in this study, GSK2586184 was well tolerated by the two patients with UC in our study. No clinically relevant changes in serum cholesterol, creatinine or liver enzymes were observed during treatment in either patient with UC. However,

given the limited number of patients treated in this study, all results on clinical efficacy and safety should be interpreted with caution. GSK2586184 ameliorated clinical parameters and biomarkers for UC, including total and partial Mayo scores, Mayo endoscopic sub-score, UCEIS and faecal calprotectin. In addition, in biopsy material, histopathology improved after treatment.

GSK2586184 was developed for various indications, including SLE, psoriasis and UC as reported here. The SLE study was halted at 50 patients after the interim analysis indicated that GSK2586184 did not induce the predicted 40% reduction in the percentage inhibition of interferon transcriptional biomarker expression.⁶ In this study, a total of 10 Serious Adverse Events (SAEs) were reported among 8 of the 39 subjects who received GSK2586184. Seven of these eight subjects experienced one SAE and one subject experienced three SAEs (drug-induced liver injury, upper abdominal pain and fever). All of the SAEs were reported as drug related except for urinary tract infection and blighted ovum. Elevated liver enzymes were detected in six patients. In four of these patients, elevated Alanine Aminotransferase (ALT) levels were normalised within 2–4 weeks after discontinuation of the drug. Also, one confirmed and one suspected case of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) occurred after exposure to the drug. In both patients, liver abnormalities and DRESS symptoms resolved within 18 to 22 days after onset. A dose-dependent increase of HDL serum cholesterol levels was observed, however without elevation

of LDL levels as reported in tofacitinib studies. Several other inhibitors targeting JAK1 and JAK2 are under clinical investigation for a wide array of indications, including ruxolitinib, baricitinib and momelotinib.^{13–15} Given the lack of reports on DRESS observed in these studies, this phenomenon is likely to be SLE specific or a result of interactions with concomitant medication. The mechanism behind this remains unclear at this point and this JAK1-selective inhibitor will not be further developed for SLE.⁶

In psoriasis, the phase II study investigating safety and efficacy of GSK2586184 was completed. A total of 67 patients were randomised to receive oral placebo or a dose ranging from 100 to 400mg twice daily during 12 weeks. Clinical efficacy, defined by the proportion of patients achieving a 75% reduction in their psoriasis severity at week 12, was achieved in 57% of the patients receiving the 400mg dose versus none of the patients receiving placebo. In this study, two drug-related serious adverse events occurred. One patient in the 400mg arm developed a ureteral calculus and one patient in the 100mg arm developed severe thrombocytopenia, which was reversed after discontinuation. No clinically significant changes in serum creatinine, cholesterol levels or haematology variables were observed.¹⁶

Although no other data regarding the use of selective JAK inhibitors in UC is available, a recent study evaluated the use of a JAK1 selective inhibitor (FITZROY study) in Crohn's disease (CD). In this study, 174 patients were randomised to receive 200mg of the JAK1 selective inhibitor filgotinib or placebo for 10 weeks. Filgotinib (Galapagos, Mechelen, Belgium) induced clinical remission, defined as a Crohn's Disease Activity Index of below 150 points, in 47% of patients, compared with a 23% remission rate in the patients receiving placebo ($p=0.0077$). Rates of infectious adverse events did not differ between patients receiving filgotinib and patients receiving placebo (30% vs 23%). Four in 152 patients (3%) receiving the drug experienced a serious infection versus none in the placebo group. Similar incidences in early discontinuations and serious adverse events were observed, with the majority related to worsening of disease.¹⁷ A phase II trial evaluating the efficacy of another selective JAK1 inhibitor in CD (ABT-494, AbbVie, Chicago, Illinois, USA) is currently ongoing, but has yet to report any results.

Despite the SAEs that occurred in the GSK2586184 development programme, JAK1 selective inhibition has shown promising results in CD and other inflammatory disorders. Together with the data reported here on the efficacy of selective JAK1 inhibition in UC, JAK1 remains an attractive therapeutic target in inflammatory bowel disease, and further investigation is warranted.

Learning points

- ▶ GSK2586184 is the first oral JAK1 selective inhibitor investigated in two patients with ulcerative colitis (UC) and was well tolerated.
- ▶ This case report demonstrates the potential of an oral JAK1 selective inhibitor to induce clinical and endoscopic response in two patients with UC.
- ▶ This study was discontinued after two inclusions due to safety concerns with the agent in a parallel trial for systemic lupus erythematosus, most likely a disease-specific phenomenon.
- ▶ JAK1 remains an attractive therapeutic target in inflammatory bowel disease and further investigation is warranted.

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Contributors LCSDV was responsible for conduct of the study and drafting the article. VJL, KJH and GRD'H were responsible for critical revision and final approval of the version to be submitted for publication. All authors were involved in the original conception and planning of the study.

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