NOVEL ORAL TARGETED THERAPIES IN INFLAMMATORY BOWEL DISEASE

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Summary

Background

There is a great unmet clinical need for efficacious, tolerable, economical and orally administrated drugs for the treatment of inflammatory bowel disease (IBD). New therapeutic avenues have become possible including the development of medications that target specific genetic pathways found to be relevant in other immune mediated diseases.

Aims

To provide an overview of recent clinical trials for new generation oral targeted medications that may have a future role in IBD management.

Methods

Pubmed and Medline searches were performed up to 01/03/18 using keywords: 'IBD', 'UC', 'CD', 'inflammatory bowel disease' 'ulcerative colitis', Crohn's disease' in combination with 'phase', 'study', 'trial', and 'oral'. A manual search of the clinical trial register, article reference lists, abstracts from meetings of *Digestive Disease Week, United European Gastroenterology Week* and *ECCO congress* were also conducted.

Results

In randomised controlled trials primary efficacy endpoints were met for tofacitinib (JAK 1/3 inhibitor-phase III), upadacitinib (JAK 1 inhibitor-phase II) and AJM-300 (α4-integrin antagonist-phase II) in ulcerative colitis. Ozanimod (S1P receptor agonist-phase II) also demonstrated clinical remission. For Crohn's disease, filgotinib (JAK1 inhibitor-phase II) met primary endpoints and laquinimod (quinolone-3-carboxide small molecule-phase II) was also efficacious. Trials using mongersen (SMAD7 inhibitor) and vidofludimus (dihydroorotate dehydrogenase inhibitor) have been halted.

Conclusions

This is potentially the start of an exciting new era in which multiple therapeutic options are at the disposal of physicians to treat IBD on an individualised basis. Head-to-head studies with existing treatments and longer term safety data are needed for this to be possible.

Keywords

Inflammatory bowel disease, Crohn's disease, ulcerative colitis, immunotherapy

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic and progressive immune mediated condition of the gastrointestinal (GI) tract influenced by both genetic and environmental factors. Often patients require lifelong medical therapy and others surgery depending on disease severity. A meta-analysis showed the 5 and 10 year risk for needing surgery for Crohn's disease (CD) and ulcerative colitis (UC) was 33.3%, 46.6%, 11.6 and 15.6% respectively (1). Approximately 25% of CD patients will require additional intestinal surgery within five years of their first (2). The risk of requiring surgery after diagnosis has decreased over the past six decades but remains a significant burden (3). This has both financial implications and a

negative impact on a patient's quality of life (4). For a considerable duration, the mainstay of medical treatment for IBD has been the use of steroids for the induction of remission and immunomodulatory drugs such as azathioprine, mercaptopurine and methotrexate to maintain remission (5). However, since 1997 when Targan *et al* reported the first randomised controlled trial (RCT) to show the effectiveness of the anti-tumour necrosis factor (TNF) infliximab, there has been a paradigm shift in IBD management. This has led to the introduction of a number of anti-TNF and other biological agents such as adalimumab, certolizumab, golimumab, ustekinumab and vedolizumab (6-15).

During the course of this disease, many patients are treated with various immunosuppressive medications either due to a lack of efficacy, loss of response or drug intolerance (16). Up to a third of patients treated with anti-TNF therapy are primary non-responders, whilst a significant proportion (10-15% per year) lose response due to antibody formation (immunogenicity failure) (7, 17-19). These biological agents are also associated with significant adverse events, such as opportunistic infections and immune complications (20, 21). Furthermore, these drugs have the added inconvenience of parenteral administration and associated heavy health care costs (22). In a climate where hospital room capacity is limited, the use of novel oral medication could potentially increase capacity and reduce costs associated with drug infusions.

There remains a great unmet clinical need for new efficacious, tolerable, economical and orally administrated drugs. As our understanding of the major inflammatory pathways in IBD have evolved, multiple new therapeutic avenues have become possible. These include the development of new oral medications that target specific pathways found to be relevant in other immune mediated diseases. These include inhibition of cytokine cell signalling, lymphocyte influx and mast cell activity, as well as promotion of the activity of inherent

immunosuppressive pathways (23). This review provides an overview of recent clinical trials for new generation oral targeted medications that may have a role in IBD management in the future.

METHODOLOGY

A broad electronic literature search was conducted using Pubmed and Medline up to 1st March 2018 to identify the relevant studies. The following keywords were used 'IBD', 'UC', 'CD', 'inflammatory bowel disease' 'ulcerative colitis', Crohn's disease', in combination with 'phase', 'study', 'trial', and 'oral'. A manual search of the reference list of initially selected articles, abstracts from the yearly meetings of *Digestive Disease Week*, *United European Gastroenterology Week* and *European Crohn's and Colitis congress* up to 1st March 2018 was also conducted. Clinical trial status was checked on http://www.clinicaltrials.gov and http://www.clinicaltrialsregister.eu. Only articles published in English were reviewed.

POTENTIAL NEW TREATMENTS: ULCERATIVE COLITIS

α4-INTEGRIN ANTAGONIST

Integrins comprise a family of α4β heterodimeric transmembrane receptors that are constitutively expressed on leukocyte surfaces and are activated by pro-inflammatory cytokines released by activated T cells (24). The integrin family consists of at least 24 different forms representing the combination of 18 α subunits and 8 β subunits. The α-subunit determines integrin ligand specificity. The β subunit connects to the cytoskeleton and affects multiple signalling pathways (25). Inhibiting the interactions between adhesion

molecules and lymphocyte integrins has already proved to be a successful therapeutic strategy for the management of IBD (26).

Vedolizumab is a recombinant humanized, anti-α4β7 integrin monoclonal antibody, which has shown efficacy for induction and remission in both UC and CD (14, 27). Natalizumab (Biogen Idec, Massachusetts, United States) an anti-a4 integrin antibody is also effective in IBD (28, 29) and etrolizumab (Roche, Basel, Switzerland) an anti-b7 integrin antibody was investigated in a phase II trial which showed this was more likely to lead to clinical remission than placebo in UC (30). Phase III trials are currently being evaluated in IBD (31-33). A more recent development is AJM 300 (Ajinomoto Pharmaceuticals, Tokyo, Japan), an oral α4-integrin antagonist that acts by inhibiting the binding of lymphocyte integrins to adhesion molecules expressed on inflamed intestinal endothelium (34). The gut specific α4β7 integrin is expressed on lymphocytes in the gut-associated lymphoid tissue, and interacts with mucosal addressin cell adhesion molecule 1 (MAdCAM-1), whilst the non-gut specific α4β1 integrin is expressed on most leukocytes and interacts with vascular cell adhesion molecule 1 (VCAM1) (35).

AJM-300 was evaluated in a multicentre, randomised, double-blind, placebo-controlled, phase II clinical study (36), involving 102 patients with moderately active UC (Mayo scores of 6-10, endoscopic subscores ≥2, and rectal bleeding subscores ≥1) and an inadequate response or intolerable side effects to aminosalicylates or corticosteroids. 960mg dose or placebo was used three times a day for 8 weeks. The primary end-point was a clinical response (decrease in Mayo Score ≥3 points and a decrease of ≥30% from baseline, with a decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of 0 or 1) at 8 weeks. Secondary endpoint was clinical remission (Mayo Clinic score of ≤2 and no subscore >1 and mucosal healing). The latter was defined as endoscopic subscore of ≤1.

AJM-300 was more effective than placebo in delivering clinical response, remission and mucosal healing. Clinical response were 62.7% in AJM-300 group compared to 25.5% in the placebo group, (odds ratio [OR] 5.35; 95% confidence interval [CI]: 2.23-12.82; p= 0 .0002). Clinical remission rates were 23.5% in the AJM300 group and 3.9% in the placebo group (OR 7.81; 95% CI: 1.64-37.24; p=0 .0099). Mucosal healing rates were 58.8% in AJM300 group and 29.4% in placebo group (OR 4.65; 95% CI: 1.81-11.90; p=0 .0014) (36).

AJM300 was well tolerated, with no severe adverse events observed in this treated cohort. Non-significant laboratory test abnormalities were observed in the AJM300 group. One of the most concerning adverse events of α4 integrin blockade is the development of progressive multifocal leukoencephalopathy (PML), which is seen in higher frequency in patients treated with the natalizumab (37). No PML cases were observed in this study though the safety follow-up period in this study was only short-term (36). However, development opportunities for alpha 4 integrin blockers are likely to be limited due to this risk.

A phase III study is planned.

SPHINGOSINE RECEPTOR MODULATOR

Sphingosine 1-phosphate (S1P) is a sphingosine-derived circulating phospholipid that binds to five G-protein-coupled receptors (GPCRs), termed S1P1-5 (38). S1P receptor's function to regulate processes such as migration, adhesion and endocytosis. They also mediate angiogenesis, vascular permeability and trafficking lymphocytes (39, 40). Ozanimod (RPC1063; Celgene, New Jersey, USA) is an oral sphingosine receptor agonist under development for the treatment of UC and multiple sclerosis. Ozanimod stimulation of

S1P1 on lymphocytes results in receptor internalization and a functional antagonism that causes sequestration of lymphocytes in peripheral lymphoid organs and reduction in circulating lymphocytes. In addition, the activation of S1P receptors on endothelial cells tightens the endothelial barrier, further restricting T cell movement into the intestine (41).

Ozanimod was evaluated in a randomised, double-blind, placebo-controlled phase II trial the TOUCHSTONE study (42). 197 patients with moderate-to-severe active UC (Mayo score ≥6 and endoscopy subscore ≥2) were randomised in approximately 1:1:1 fashion to once daily 1 mg ozanimod (n=67), 0.5 mg ozanimod (n=65) or placebo (n=65) for 8 weeks (the induction phase). The primary endpoint was clinical remission (defined as Mayo score ≤2 and no subscore > 1) at week 8. The exploratory secondary end points were clinical response (defined as reduction in Mayo score of ≥3 points and ≥30% from baseline, with a decrease in the rectal bleeding score of ≥1 or a rectal bleeding score ≤1) at week 8. Mucosal healing (defined as endoscopy subscore ≤1) and other objective markers such as CRP and faecal calprotectin were measured to examine for changes from baseline. Clinical remission was slightly higher in the 1mg group when compared to placebo (16% vs 6%, p=0.048). There was no significant difference in the proportion of patients with a clinical response or endoscopic mucosal healing. Ninety one patients completed a 32 week double blind maintenance phase but there was no significant difference between clinical remission, response and mucosal healing. Ozanimod did not show an adequate efficacy signal and the follow up period was too short to fully assess drug safety. Adverse events were comparable in the three groups; one patient developed a sinus bradycardia and first degree AV block leading to discontinuation of the drug and four patients had elevated liver enzymes (42). The long-term follow up of patients involved in the TOUCHSTONE study demonstrated

treatment with ozanimod to be safe, efficacious and well tolerated in patients with moderate-to-severe UC followed up to two years (43).

Initial results of a further phase II trial of 69 patients treated with ozanimod for moderate-to-severe CD demonstrated a clinical improvement by week 4 and endoscopic improvement by week 12 (44, 45). A phase III trial in moderate-to-severe UC (46) and a phase III trial assessing efficacy and safety in UC (47) are currently ongoing.

Etrasimod (APD334; Arena Pharmaceuticals, California, United States) is a similar compound which selectively targets S1P1, S1P4 and S1P5 in in-vitro assays thus also has the potential for immune cell modulation (48). Etrasimod is currently been evaluated in a randomised, parallel phase II study in patients with UC (49, 50). Another S1P receptor target that has completed a phase II study is amiselimod (MT-1303; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) in CD (51). However, the development of amiselimod has recently been discontinued.

PHOSPHODIESTERASE 4 INHIBITOR

Phosphodiesterase 4 (PDE4) is an enzyme responsible for lysis of cyclic adenosine monophosphate (cAMP) in inflammatory cells. Apremilast (CC-10004, Celgene, New Jersey, USA) is an oral small-molecule inhibitor of PDE4 modulating pro- and anti-inflammatory mediators (52). A phase II randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of apremilast has recently completed recruitment. 170 patients with active UC (Mayo score ≥6 to ≤11, Mayo endoscopic score of ≥2) who have previously failed conventional treatment but were biologic naïve were recruited. Patients were randomised to 60mg/day, 80mg/day or placebo for 12 weeks. The primary endpoint was the proportion

of patients in clinical remission (Mayo score ≤2 and no subscore > 1) at 12 weeks. The secondary endpoint was the proportion of patients with clinical response (reduction in Mayo score of ≥3 points and ≥30% from baseline, with a decrease in the rectal bleeding score of ≥1 or a rectal bleeding score ≤1) at 12 weeks.

A significant number of patients treated with 60mg/day were in clinical remission when compared to placebo (31.6% vs 13.8%, p≤0.05). Clinical response was significantly higher in the 80mg/day group when compared with placebo (67.3% vs 46.6%, p≤0.05). In the 12 week follow up, the 60mg/day dose showed the most efficacy when compared with placebo. There were no new safety reports (53). This phase II study is currently still active: patients will receive a further 40 weeks of treatment with either 60mg/day or 80mg/day of apremilast and be followed up to week 52 (54).

MAPK INHIBITORS

Mitogen-activated protein kinase (MAPK) superfamily plays an essential role in eukaryotic cell regulation to produce pro-inflammatory cytokines. P38α, JNKs and ERK1/2 have been shown to be significantly activated in the inflamed colonic mucosa of IBD patients (55).

RDP58 (SangStat Medical Corporation, California, USA), also known as delmitide acetate, is a drug that disrupts cell signalling which is responsible for activating p38 MAPK, JNK, and I kappa kinase (IKK) (56). Travis *et al* first evaluated the efficacy, safety and tolerability of RDP58 in a phase II trial (57). Data for two studies was reported for patients with mild-to-moderate UC (Simple Colitis Activity Index (SCCAI) score 4 to 9 and active disease at sigmoidoscopy (Baron Score≥ 1) within this trial. In the first study, 34 patients were

randomised (2:1) to RDP58 100mg or placebo. In the second study, 93 patients were randomised (1:1:1) to receive RDP58 200mg, RDP 300mg or placebo.

No statistical difference was observed in the primary and secondary endpoints between RDP58 100mg and placebo. In the second study, treatment success was higher with increasing doses: 71% and 72% for the 200mg and the 300mg dose respectively when compared to 43% for placebo (p = 0.016). Adverse events were similar between RDP58 300mg and placebo (57). No further clinical trials evaluating RDP58 in UC are planned.

MODIFIED RELEASE PHOSPHATIDYCHOLINE

UC patients have been found to have a low intrinsic phosphatidylcholine content that reduces intestinal mucus barrier function, making it more susceptible to inflammation and ulceration (58, 59). An improved, modified release phosphatidylcholine (LT02; Dr. Falk Pharma GmbH, Freiburg, Germany) and the first oral therapy targeting stabilisation of gut barrier was evaluated in a double blinded, randomised, placebo controlled phase II study. 156 UC patients with an inadequate response to mesalazine, SCCAI ≥ 5 and bloody diarrhoea were treated with placebo, 0.8, 1.6 or 3.2 g of phosphatidylcholine. The primary endpoint was defined as a >3 point drop in SCCAI from baseline to the end of treatment. SCCAI score change for placebo, 0.8g, 1.6g and 3.2g was 33.3%, 44.3% and 51.7% respectively. The 3.2g dose was statistically superior when compared to placebo at 51.7% compared to 33.3% (p=0.03). Histological remission for placebo and all phosphatidylcholine doses was 20% compared to 40.5% (p=0.016). Phosphatidylcholine was found to be safe (60). However, two phase III trials have since been terminated in 2017 (61, 62): the first trial because it appeared not to induce remission with the reason for termination of the second trial not yet

disclosed. Another phase III trial is still ongoing comparing phosphatidylcholine to placebo and mesalazine for maintenance of remission in UC (63).

OTHER ORAL AGENTS CURRENTLY IN EARLY DEVELOPMENTAL STAGE

Free fatty acids (FFA) act as energy source but also important for metabolic and inflammation regulation. FFA2 receptor and other G protein receptors are activated by FFA. Knockout mice studies suggest FFA2 has important roles in controlling inflammation (64). GLPG0974 (Galapagos NV, Mechelen, Belgium) is a selective antagonist of FFA2 and was shown to be safe and tolerable in healthy subjects (65). A randomised, exploratory, double blind, phase II trial evaluating the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of GLPG0974 in UC has been completed and results are awaited (66).

There are many other potential new agents at varying stage of developments. LYC-30937 (Lycera Corp, Minnesota, United States) is an oral ATPase modulator currently in phase II studies evaluating its use in UC (67, 68). TOP-1288 (Topivert Pharma Ltd, London, England) is a nonselective kinase inhibitor that has recently been evaluated in a rectal solution in UC (69) and now an oral administered phase I study on healthy subjects has recently been completed (70). GSK2982772 (GlaxoSmithKline, Brentford, England) is a RIP1 kinase inhibitor currently being evaluated in a phase II study (71). Rosiglitazone (GlaxoSmithKline, Brentford, England) a PPAR-γ agonist has been shown to be efficacious in mild to moderate ulcerative colitis in a phase II trial (72). A randomised, cross over placebo controlled phase II trial of VB-201 (VBL Therapeutics, Tel Aviv, Israel), a small oxidized phospholipid molecule in UC has recently been completed but as this study did not meet its primary endpoints there are no plans to continue drug development (73). Finally, AVX-470 (Avaxia Biologics,

Massachusetts, United States) is an orally administered anti-TNF agent that seems promising after the completion of a phase I study (74).

POTENTIAL NEW TREATMENTS: CROHN'S DISEASE

QUINOLONE-3 CARBOXIDE

Laquinimod (TV-5600; Teva Pharmaceutical Industries Ltd, Petah Tikva, Israel) is an oral quinolone-3-carboxide small molecule that has shown efficacy in treating multiple sclerosis (MS) (75, 76) and may have a potential role in treating Huntington's disease (77) and lupus nephritis (78). Both animal and *in vitro* experimental studies have alluded to various mechanisms by which this drug interacts with the immune and nervous system in MS. Laquinimod has been shown to decrease pro-inflammatory immune cells and the activation of anti-inflammatory genes. It also exhibits effects on regulatory T cells by promoting their differentiation (79). A study in experimental autoimmune encephalomyelitis (EAE) (an animal model of MS) has found that quinolone-3-carboxamides inhibited the interaction of S100A9 with two receptors, toll-like receptor 4 and receptor of advanced glycation end products, thereby preventing the downstream release of inflammatory cytokines, including tumour necrosis factor α (TNFα) and interleukin (IL)-1 (80). Laquinimod has also been shown to increase levels of the anti-inflammatory cytokines IL-10 and transform growth factor β (TGFβ) in both T and B cells, suppressing immune activity and downregulating the immunogenicity of the dendritic cell response (81). Laquinimod treatment has been shown to inhibit the ability of the CCR7-binding chemokine, CCL21, to stimulate very late antigen-4 (VLA-4) adhesiveness to its natural ligand, vascular cell adhesion molecule-1 (VCAM-1) in

splenic T cells isolated from immunized mice (82) and reduce the *in vitro* secretion of several chemokines participating in the recruitment of leucocytes to inflammatory tissue sites (83).

Laquinimod was evaluated in an exploratory phase IIa multicentre, randomised, double blind placebo-controlled and dose-finding trial. 117 patients were randomised to laquinimod doses of 0.5, 1, 1.5 or 2 mg/day, in a 1:1:1:1 fashion, while 63 patients were exposed to placebo for 8 weeks. CDAI scores, CRP, and faecal calprotectin were recorded at week 0, 2, 6, 8 and 12. Treatment failures (TF) were defined as patients who were not responding, needed biologic, immunosuppressive therapy or surgery. Clinical remission was defined as (CDAI <150 and no TF). Endpoints were to assess safety profile, dosing and the number of patients in clinical remission (CDAI <150 and no TF). Other endpoints included the number of patients with a clinical response with a reduction of CDAI score by ≥70 & ≥100 points from baseline, in remission, no TF and a mean change in objective markers from baseline. Although this study was not powered for efficacy, the lowest dose 0.5mg/day had the highest response rate when compared to placebo. 48% were in remission at the end of week 8 compared to 15.9% in the pooled placebo group. CDAI 70 and 100 were 62% and 55% respectively in the 0.5mg/day group compared with 35% and 32% respectively of patients exposed to placebo. The higher doses showed similar responses to placebo (84). D'Haens *et al* also investigated whether changes in plasma concentrations could explain the clinical improvement seen in lower doses. Laquinimod concentration reached its maximum within one hour of administration and remained at a steady plasma concentration throughout the 24 hour period. The pharmacokinetics seems to be linear in CD patients in the dose range 0.5-2mg/day. The pharmacokinetics could not explain the improved response at lower dose (85).

Laquinimod could be used safely for 8 weeks at all doses with an adverse event profile similar to placebo. Incidence of adverse events in all doses was 86.2%-96.7% vs placebo 82.5% (84, 85).

Phase IIb/III trials are currently awaited.

ANTISENSE OLIGONUCLEOTIDE SMAD7 INHIBITOR

Reduced tissue growth factor-β receptor type I (TGF-β1) cytokine activity due to overexpression of SMAD7 is seen in individuals with IBD (86, 87). Mongersen (GED-0301; Celgene, New Jersey, USA) is a new class of drug (86) which acts to reinstate the TGFβ1 immunosuppressive pathway (88).

Mongersen's efficacy and safety was evaluated in a multicentre, randomised, double-blind, placebo-controlled phase II trial involving 166 patients with moderate-to-severe CD (Crohn's Disease Activity Index 220-400). Participants were randomised to receive placebo or daily mongersen for 14 days. Clinical response was significantly higher in the 160mg and 40mg/day groups when compared to placebo (65% and 55% vs 10%, $p<0.001$ (89). A post-hoc analysis of this trial showed neither an elevated CRP nor duration of disease impacted on efficacy. No association was seen between baseline CDAI and remission rates but the 40mg dose showed the lowest remission rates with CDAI ≥260 (90).

However, a significant limitation of the Monteleone *et al* study was that the inclusion criteria were based on CDAI score and with no objective endoscopic measure of disease activity. At baseline, 39% of participants had a normal CRP (91) implying low disease activity in the exposed population, so patients were not reflective of the usual moderate-to-severe

patients. Moreover the primary endpoint was clinical remission only as measured through CDAI and this was only measured at 28 days. As such, no data are available on long-term clinical remission, endoscopic remission or safety.

In a recent noteworthy turn of events, Celgene has recently terminated their Phase III REVOLVE and SUSTAIN clinical trials of mongersen following recommendation from the external Data Monitoring Committee. This decision was based upon the lack of emerging benefit but not safety findings during their recent review of interim unblinded data. The planned Phase III DEFINE study in Crohn's will also not be initiated. However, a phase II trial in UC has recently completed recruitment (92). Celgene is waiting to review the full dataset from this trial for UC to determine the next steps.

POTENTIAL NEW TREATMENTS: CROHN'S DISEASE AND ULCERATIVE COLITIS

JANUS KINASE INHIBITORS

Janus kinases (JAKs) are a family of intracellular protein tyrosine kinases: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). These are crucial to the downstream regulation of inflammatory mediators. Transcription factor STATs (signal transducer and activation of transcription) are activated by the binding of transmembrane receptors. A number of cytokines deliver their function by activating the JAK-STAT pathway thus having an important role in the immune system and development of immune mediated disorders (93, 94). JAK inhibition results in suppression of B and T cells but retains regulatory T cell function, therefore, is an important target in IBD (95, 96).

Tofacitinib

Tofacitinib (CP-690,550; Pfizer, New York City, USA) is a JAK 1 and 3 inhibitor that has been studied in autoimmune conditions, including rheumatoid arthritis and psoriasis with a good overall efficacy and an acceptable safety profile (97-99).

The use of tofacitinib in UC was evaluated in a multi-centre, double-blind, placebo-controlled, dose-ranging phase II study, including 194 adults with moderate-to-severe active UC (Mayo score ≥ 6 and endoscopic subscore ≥ 2) who had failed conventional therapy (100). Stable doses of mesalamine or prednisolone at a maximum of 30mg were permitted during the trial period. Patients were randomised to tofacitinib 0.5, 3, 10, or 15 mg or placebo twice daily for 8 weeks. The primary efficacy end point was a clinical response, defined as an absolute decrease in Mayo score of ≥ 3 points and relative decrease ≥30%, with an accompanying decrease in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1. Of the secondary end points, clinical remission was defined as Mayo score ≤2 with no individual subscore >1 at week 8, endoscopic response was defined as a decrease from baseline in the subscore ≥1 at week 8, and endoscopic remission was defined as endoscopy subscore of 0 at week 8. The only statistical significant clinical response was with the 15mg twice a day dose when compared to placebo (78% vs 42%, $p<0.001$). Clinical remission was 13%, 33%, 48%, and 41% at 0.5mg ($p=0.76$), 3mg $p=0.01$), 10 mg ($p<0.001$), and 15 mg ($p<0.001$), respectively when compared with 10% for placebo. Tofacitinib was well tolerated and reasonably effective in moderate-to-severe UC (100). Tofacitinib is also associated with dose-dependent improvement in health related quality of life measures (101). Faecal calprotectin showed a moderate correlation with clinical and endoscopic outcomes in patients receiving tofacitinib. A cut off value of 150 mg/kg showed a fair to good accuracy in classifying these outcomes (102).

Sandborn *et al* recently reported the use of tofacitinib as induction and maintenance therapy in UC. A number of randomised, double blind, placebo controlled phase III trials were conducted. The OCTAVE Induction 1 and 2 trials included patients with moderate-to-severe UC (Mayo score ≥6, endoscopic subscore ≥ 2 and rectal bleeding subscore ≥ 2). Patients with previous treatment failures or unacceptable side effects to anti-TNF or immunomodulatory drugs were included in these studies. Concomitant medications included prednisolone <25mg/day and oral aminosalicylates. In the first two trials, 598 and 541 patients were randomised (4:1) to induction therapy (10mg twice a day) or placebo for 8 weeks. Primary endpoint of clinical remission (a total Mayo score of $\leq$2, with no subscore >1 and a rectal bleeding subscore of 0) at 8 weeks was 18.5% in tofacitinib group versus 8.2% in the placebo (p=0.007) in the OCTAVE 1 trial. In the OCTAVE 2 trial this was 16.6% versus 3.6% (p<0.001). In the OCTAVE 1 trial, the 10mg group mucosal healing rate was 31.3% compared to placebo 15.6% (p<0.001). In the OCTAVE 2 trial, this was 28.4% vs 11.6% (p<0.001).

Patients who achieved a clinical response (reduction total Mayo score ≥3 points, rectal bleeding score ≥1 or absolute rectal bleeding subscore of 0 or 1) in the OCTAVE 1 and 2 were eligible to participate in the third OCTAVE Sustain trial. Patients were randomised (1:1:1) to receive 5mg, 10mg or placebo twice a day for 52 weeks. The primary endpoint was remission at 52 weeks. Secondary endpoints were mucosal healing at 52 weeks and sustained steroid free remission (both at 24 and 52 weeks). In this trial clinical remission at 52 weeks were 34.3% in 5mg group, 40.6% in the 10mg group compared with 11.1% in the placebo (p<0.001 for both comparisons). Mucosal healing occurred in significantly more patients at 52 weeks. In the 5mg, 10mg and placebo this was 37.4%, 45.7% and 13.1% (p<0.001) respectively. Sustained steroid free remission was 34.4%, 47.3% and 5.1%

(p<0.001) in the 5mg, 10mg and placebo group respectively. These results demonstrate that tofacitnib is more effective as an induction and maintenance agent than placebo (103). The 3 year interim efficacy and safety data from the OCTAVE 1, 2 and OCTAVE Sustain studies open label long-term extension study reported a similar safety profile to those observed with rheumatoid arthritis patients and a sustained efficacy with 5mg and 10mg twice a day dose (104). Currently one phase I trial (105) and a phase III trial (106) are underway for tofacitnib in UC.

However in patients with CD tofacitinib did not exhibit a significant clinical remission and response rate. The use of tofacitinib in CD was evaluated in a multi-centre, double-blind, placebo-controlled, phase II trial including 139 patients with moderate–to-severe CD (CDAI 220-450). Patients were randomised to (1, 5 or 15 mg twice a day) or placebo for 4 weeks. The primary and secondary endpoints were the proportion of clinical responders at week 4 (CDAI of ≥70 points) and clinical remission at 4 weeks (CDAI <150) respectively. There was no significant difference in the primary and secondary endpoints. It is unclear whether these findings are due to the high placebo response rate or difference in the immunopathology CD and UC (107). Panés *et al* reported a recently conducted phase IIb trial in which CD patients were randomised to 5 mg (n=86), 10 mg twice (n=86) or placebo (n=91) twice a day for 8 weeks. There was no significant difference in remission rates reported despite the longer treatment duration. The clinical response was slightly significantly higher as was CRP reduction in the tofacitinib group when compared to placebo. There was no change in in faecal calprotectin levels (108). Panés *et al* later reported on two randomised, double-blind, placebo-controlled, multicentre phase IIb studies of 180 patients with moderate–to-severe CD. Clinical remission was not significantly different to placebo although there were minor treatment benefits seen in change in biomarkers (secondary endpoints) (109). A number of

factors may have contributed to the high response rate seen in placebo patients. Endoscopy was not centrally read and the severity and extent of ulceration was not defined despite been part of the inclusion criteria. There was also no baseline threshold for objective markers of disease activity. Variation in endoscopic ulceration and inflammatory markers at baseline may have influence the treatment effect of drugs (109, 110).

The most commonly reported adverse events were influenza and nasopharyngitis. Neutropenia has also been reported as well as serious infections such as abscess and pneumonia. There was also a dose-dependent increase in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol which is not completely understood (87, 100, 107).

Filgotinib

Filgotinib (GLPG0634; Galapagos NV, Mechelen, Belgium) is an oral JAK1 inhibitor. Vermeire *et al* evaluated its efficacy and safety in moderate-to-severe CD (CDAI 220-450) with histological evidence of active inflammation in a randomised, double-blind, placebo-controlled phase II study. 174 patients were randomised (3:1) to filgotinib 200 mg once a day or placebo for 10 weeks. Patients were then assigned according to their CDAI clinical responder status to filgotinib 100mg, 200mg or placebo once a day for a further 10 weeks. The primary endpoint was clinical remission (CDAI ≤150) at 10 weeks. Secondary endpoints included clinical remission at weeks other than week 10; endoscopic response and clinical response (change from baseline in overall CDAI score and in CDAI component subscores). Clinical response was achieved in 59% in the filgotinib group compared to 41% in placebo (p=0.453). Clinical remission was 47% compared to 23% in placebo (p=0.077). The safety profile was satisfactory and clinical remission was induced in the filgotinib group. Response

rate was almost twofold higher in patients naïve to anti-TNFs compared to those exposed to at least one. The data suggest that filgotinib could be effective in both anti-TNF naïve and exposed (111). A recent post hoc analysis of this phase II study showed that clinical remission is still seen in CD regardless of disease location and duration (112). Currently phase III trials are underway in CD and UC (113-116).

Upadacitinib

Sanborn *et al* evaluated the safety and efficacy of a JAK 1 inhibitor upadacitinib (ABT-494; AbbVie, Illinois, United States) in CD patients who had inadequate response or intolerant of immunomodulators or anti- TNF therapy in a phase II, multicentre, randomised, double blind placebo controlled trial. This trial included 220 patients with moderate–to-severe CD (CDAI 220-450). Patients were randomised to upadaciitinib 3, 6, 12, 24mg twice a day, 24mg once a day or placebo for 16 weeks. Concomitant steroid use was allowed and tapered from week 2. The primary endpoints were clinical remission at week 16 (stool frequency (SF) ≤1.5 or abdominal pain (AP) ≤1, and both no worst from baseline) and endoscopic remission at week 12/16 (Simplified Endoscopic Score (SEC) for CD ≤4 and ≥2 point reduction from baseline, no subscore >1). The overall dose response relationship was also investigated. Significantly more patients achieved clinical remission with 6mg twice a day dose when compared with placebo (27% vs 11% p≤0.05). There was a significant dose relationship for endoscopic remission when doses 12mg, 24mg twice a day and 24mg once a day compared to placebo (8% p≤0.05 , 22% p≤0.001, 14% p≤0.01 and 0% respectively). This study demonstrated both clinical and endoscopic benefit with 6mg doses and above (117, 118). Upadacitinib use also results in a significant and sustainable reduction in markers of inflammation (119). Upadacitinib is also currently being evaluated in phase II trials in UC (120).

Further development

A number of JAK inhibitors are currently in the development phase. A Phase IIb multi-centre randomised, double blind, placebo controlled, parallel group, dose response trial evaluating the safety and efficacy of peficitinib (ASP015K; Astellas Pharma, Tokyo, Japan), a non-selective JAK inhibitor in moderate-to-severe active UC, has recently been completed (121). TD-1473 (Theravance Biopharma, San Francisco, US) a non-selective JAK inhibitor is currently been evaluated in a phase I trial in patients with moderate-to-severe UC (122).

DIHYDROOROTATE DEHYDROGENASE INHIBITOR

Vidofludimus (4SC AG, Martinsried, Germany) is a small molecule which acts by inhibiting activated B and T cells by blocking dihydroorotate dehydrogenase (123). It also inhibits pro-inflammatory cytokines. Herrlinger *et al* conducted a 12 week open label study to evaluate the efficacy, tolerability and safety of vidofludimus in maintaining remission in 34 steroid dependent IBD patients. Despite being relatively safe and well tolerated a further developmental phase II study was discontinued by 4SC in October 2016.(124).

Figure 1, table 1 and 2 summarise molecular targets and drug trial results.

CONCLUSION

For UC, significant treatment benefits have been seen with AJM-300, tofacitinib, and upadacitinib. Ozanimod showed some treatment benefit but the majority of endpoints were not statistically significant. All agents have a favourable short-term safety profile, with the

exception of risk of development of PML with the α4 integrin blockade of AJM-300. Phase III trials are either being planned or are underway for each to gain more data.

For CD, treatment benefits were seen with laquinimod, and phase III trials are underway. However, there is no apparent benefit with tofacitinib treatment, although the short study duration may have impacted on this. Although the phase II study of filgotinib did not shown any statistically significant benefit, phase III studies for both CD and UC are currently active.

Successful phase II but failed phase III trials, such as the mongersen trial, may have been due to high placebo response rates which are unpredictable. This could potentially be largely rectified by introducing endoscopy disease activity in the entry criteria and the use of patient reported outcomes (PRO) as outcome measures of efficacy rather than the older disease activity indices. Failed phase III after successful phase II is not very common but some examples of previous failed therapy were the Anti-IL17A cytokine therapy which was likely due to a mechanistic failure and IL10 due to dosing and drug delivery (125, 126).

Other weakness with a number of the CD trials is that they do not assess mucosal healing at endoscopy which is a desirable treatment goal that leads to increased rates of clinical remission, reduced hospitalization and surgery rates (127). Other weaknesses include low CRP at inclusion, no centrally read endoscopy, short follow up period and a lack of forced steroid tapering dosage. Rectifying these weaknesses is likely to give a true reflection of the difference between the trial agents and placebo, therefore, potentially enabling better design and success at phase III.

Novel oral targeted therapies offer exciting new avenues of treatment for IBD by targeting different parts of the inflammatory cascade. However, for targeted therapy to be achievable, a better understanding of the mechanisms leading to disease development is

crucial. A combination of increased genetic information and biomarker development is required to achieve this. New oral therapies have the potential to provide a more acceptable, convenient treatment on an individualised basis. This may allow for the introduction of more targeted immunosuppression thus reducing inflammation, disease progression and associated complications which ultimately lead to an improved quality of life. Moreover, a better understanding of the disease pathogenesis might allow a strategy to combine targeted therapies hence ultimately achieving the holy grail of truly personalising therapies in IBD.

However, long term infection and malignancy rates also need to be better determined in large prospective studies in addition to side effects, hospital admission rates and other significant costs. There is a growing need for long phase IV studies for these drugs in development and the use of registries like TREAT and PIANO to assess the long-term safety of these drugs. Potentially, the development of more targeted therapies may also mean that complications can be avoided in susceptible individuals compared to the current blanket approach to treatment.

At present, the majority of IBD patients respond to some form of current therapy but the loss of response is a problem. Although population-based studies are suggesting a decrease in surgical rates for both CD and UC (3, 128), better and more targeted therapies are needed to sustain this paradigm shift world-wide. There is presently no head-to-head comparison between presently licenced therapies and future targeted therapies to allow a better understanding of when these targeted therapies should be introduced in present treatment algorithms.

Moreover, there are no clear predictive biomarkers to identify the subgroups of IBD patients that will respond to these new targeted therapies. If these agents are successful, then this will lead to an exciting new era of personalised and precise therapy in IBD, as is already the case in other areas of medicine.

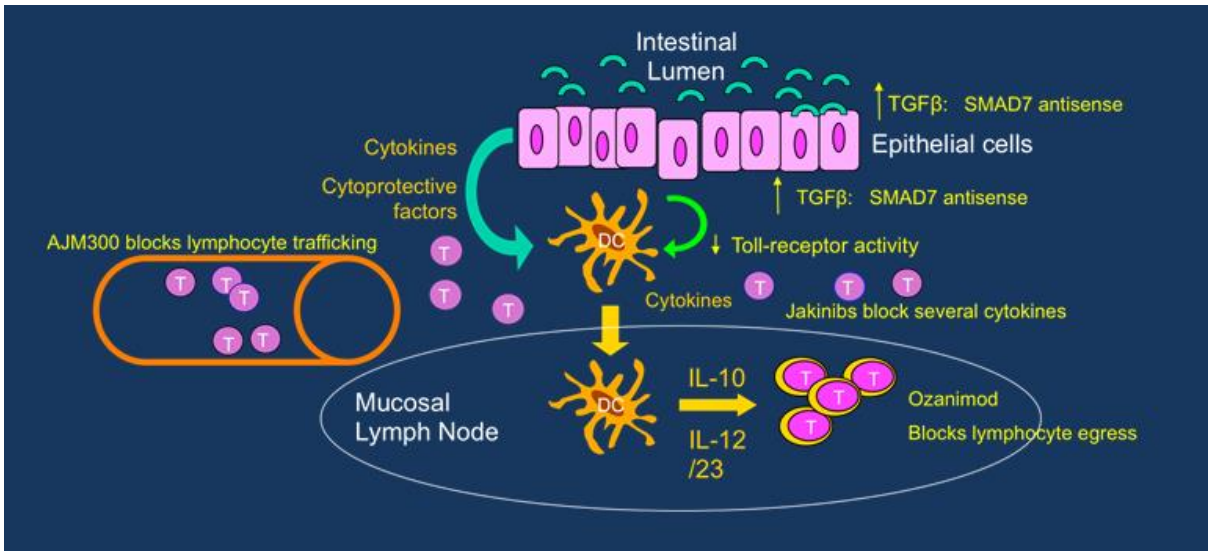

Figure 1: Summary of oral drugs and targets

Drug mechanisms and cellular targets. T= T lymphocytes, DC=Dendritic cells, IL-Interleukin, TGFβ= Tissue growth factor-β receptor.

Table 1: Summary of trials in ulcerative colitis

Drug trial	Clinical response*	Clinical remission**	Summary and safety
Tofacitinib *Janus kinase 1 and 3 inhibitor* *N= 194* *Phase II*	• Placebo 42% • 0.5 mg 32% • 3 mg 48% • 10 mg 61% • 15 mg 78% (p<0.001)	• Placebo 10% • 0.5 mg 13% (p=0.76) • 3 mg 33% (p=0.01) • 10 mg 48% (p<0.001) • 15 mg 41% (p<0.001)	Dose-related treatment benefit with no severe adverse effects.
AJM-300 *Anti α4-integrin* *N=102* *Phase II*	• Placebo 25.5% • 960 mg tds 62.7% (p=0.0002)	• Placebo 3.9% • 960 mg tds 23.5% (p=0.0099)	Significant treatment benefit with no severe adverse events
Ozanimod *S1P receptor agonist* *N= 197* *Phase II*	• Placebo 37% • 0.5 mg 54% • 1.0 mg 57% p=ns	• Placebo 6% • 0.5 mg 14% • 1.0 mg 16% (p=0.048).	Dose-related treatment benefit with no severe adverse effects. Mild elevation in transaminases seen in minority.
Apremilast *Phosphodiesterase 4 inhibitor* *N=170* *Phase II*	• Placebo 46.7% • 60mg/day 61.4% • 80mg/day 67.3% (p≤0.05)	• Placebo 13.8% • 60mg/day 31.6% (p≤0.05) • 80mg/day 21.8%	Treatment benefit at 12 weeks with no new safety concerns
Phosphatidylcholine *Modified release phosphatidylcholine* *N=156* *Phase II*	• Placebo 60% • 0.8g/day 77.5% • 1.6g/day 73.2% • 3.2g/day 82.9% (p=0.03)	• Placebo 15% • 0.8g/day 27.5% • 1.6g/day 22% • 3.2g/day 31.4% (p=0.09)	Improvement in disease activity and acceptable safety Two phase 3 studies have been discontinued, one ongoing

**Clinical response: absolute decrease in Mayo score of ≥ 3 points and relative decrease ≥30%, with an accompanying decrease in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1, at week 8.LT-02: SCCAI decrease ≥ 2.*

***Clinical remission: Mayo score ≤2 with no individual subscore >1 at week 8. LT-02: < 3 mean SCCAI and "blood in stool" subscore of 0.*

tds= three times a day

ns= non-significant

Table 2: Summary of trials in Crohn's Disease

Drug trial	Clinical response*	Clinical remission**	Summary and safety
Laquinimod *quinolone-3-carboxide small molecule* *N=117* *Phase IIa*	• Placebo 31.7% • 0.5 mg/day 55.2% • 1.0 mg/day 40% • 1.5 mg/day 27.6% • 2.0 mg/day 27.6% p=ns	• Placebo 15.9% • 0.5 mg/day 48.3% • 1.0 mg/day 26.7% • 1.5 mg/day 13.8% • 2.0 mg/day 17.2% p=ns	Treatment benefit seen for 0.5mg dose, with safety profile similar to placebo. Phase IIb/III trials awaited.
Filgotinib *JAK1 inhibitor* *N=174* *Phase II*	• Placebo 41% • 200mg/day 59% (p=0·0453)	• Placebo 23% • 200mg/day 47% (p=0·0077)	Induces remission in CD. Acceptable safety profile
Upadacitinib *JAK1 inhibitor* *N=220* *Phase II*	• Placebo 32% *** • 12mg/day 57% p≤0.01 • 48mg/day 61% p≤0.01	• Placebo 11% **** • 12mg/day 27% p≤0.05	Induces remission in CD in doses 12mg/day and higher. Acceptable safety profile
Mongersen *Antisense oligonucleotide* *SMAD7 inhibitor* *N=166* *Phase II*	• Placebo 17% • 10 mg/day 37% (p=0.04) • 40 mg/day 58% (p<0.001) • 160 mg/day 72% (p<0.001)	• Placebo 10% • 10mg/day 12% • 40mg/day 55% • 160mg/day 65% (p<0.001)	Significant dose-related treatment benefit that is sustained, with safety profile similar to placebo. Phase 3 studies have been discontinued Phase II trial in UC completed recruitment

**Clinical response: reduction of CDAI by >100 points by day 28. Filgotimib: change from baseline in overall CDAI score and in CDAI component subscores.*

*** Clinical remission: reduction of CDAI by >150 after 2 week and maintained for > 2 week. Filgotimib trial used CDAI ≤150 at 10 weeks.*

****Clinical response (_30% reduction from baseline in AP or SF with neither worse than baseline)*

*****Clinical remission at week 16 (SF ≤1.5 or AP ≤1, and both no worst from baseline)*

ns= non-significant

Acknowledgments

GWM research is supported by the National Institute for Health Research (NIHR), through the Biomedical Research Centre in Gastrointestinal and Liver Diseases at Nottingham University Hospitals NHS Trust and the University of Nottingham. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Guarantor of the article: Gordon W Moran

Author contributions: Gordon W Moran and Subrata Ghosh conceived the article; Jonathan R White and Frank Phillips wrote the article. All co-authors edited and approved the final version of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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