JAK Inhibition as a Therapeutic Strategy for Immune and Inflammatory Diseases

Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ

Nat Rev Drug Discov 2017;16(12)843–862
DOI: 10.1038/nrd.2017.201

University of Glasgow

CSF
Cytokine Signalling Forum

Background and Objectives

- Cytokines underlie the pathogenesis of many auto-immune and inflammatory diseases, which can be difficult to treat
  - Most patients are not completely responsive to currently available therapies, including monoclonal antibodies and recombinant proteins
- Janus kinases (JAKs) are essential mediators of downstream signalling for many pro-inflammatory cytokines
  - JAK inhibitors (jakinibs) can offer safe and efficacious treatment options for inflammation-driven pathologies
- This review summarizes current clinical data on jakinibs for the treatment of inflammatory and immune diseases; the development of novel second generation jakinibs is also discussed

JAK, Janus kinases

Schwartz et al. Nat Rev Drug Discov 2017;16:843–862. doi: 10.1038/nrd.2017.201

CSF
Cytokine Signalling Forum

Rationale for Clinical use of Jakinibs

- JAKs (JAK1, JAK2, JAK3 and TYK2) are receptor associated tyrosine kinases that bind directly to the intracellular domains of Type I and Type II cytokine receptors
  - First-generation jakinibs are non-selective for JAK subtypes
- Jakinibs inhibit of JAK-dependent cytokines, which are major contributors to immunopathology
  - To date, 31 kinase inhibitors have received FDA approval for the treatment of various cancers
  - Ruxolitinib, indicated for the treatment of high-risk myelofibrosis, was the first jakinib to be approved by the FDA (2011)
  - A substantial body of clinical evidence now supports the use of first-generation jakinibs in immune- and inflammatory-mediated disease

FDA, Food and Drug Administration; JAKs, Janus kinases

Schwartz et al. Nat Rev Drug Discov 2017;16:843–862. doi: 10.1038/nrd.2017.201

CSF
Cytokine Signalling Forum

Tofacitinib

- Tofacitinib (TOF) was the first jakinib to be developed for the treatment of autoimmune disease
  - Inhibits JAK3, JAK1, with some activity at JAK2
- Approved for the treatment of RA (FDA 2012; EMA 2017)
  - Clinical data from multiple clinical trials, including six Phase III studies in over 6000 patients, support the efficacy and long-term safety of TOF
- Clinical development is in progress for other conditions:
  - PsA, psoriasis, ulcerative colitis, juvenile idiopathic arthritis, alopecia areata, Crohn's disease, ankylosing spondylitis, kidney transplant, atopic dermatitis

EMA, European Medicines Agency; FDA, Food and Drug Administration; JAK, Janus kinase

Schwartz et al. Nat Rev Drug Discov 2017;16:843–862. doi: 10.1038/nrd.2017.201

CSF
Cytokine Signalling Forum

Clinical Trials of Tofacitinib: RA

Study	N	Participants	Intervention and efficacy	cDMARD	Other outcome measures
Rheumatoid Arthritis					
ORAL Solo	611	Active RA refractory to bDMARD or cDMARD	• TOF 5 mg BID (ACR20: 59%) • TOF 10 mg BID (ACR20: 65.7%) • PBO for 3 months (ACR20: 24.4%) then TOF 5 mg BID for 3 months • PBO for 3 months then TOF 10 mg BID for 3 months	Allowed: anti-malarials, prednisone <10 mg daily, NSAIDs	ACR50/70, HAQ-DI, DAS28-ESR, DAS28-CRP, FACIT
ORAL Step	399	Moderate-to-severe RA, refractory to TNFi	• TOF 5 mg BID (ACR20:41.7%) • TOF 10 mg BID (ACR20: 48.1%) • PBO for 3 months (ACR20:24.4%) then TOF 5 mg or 10 mg BID for 3 months	Required: MTX Allowed: prednisone ≤10 mg daily, NSAIDs	ACR50/70, HAQ-DI, DAS28-ESR, DAS28-CRP, FACIT, SDAI
ORAL Standard	717	Active RA refractory to MTX	• TOF 5 mg BID (ACR20:51.5%) • TOF 10 mg BID (ACR20:52.6%) • Adalimumab 40 mg BIW (ACR20:47.2%) • PBO for 3 months (ACR20:28.3%) then TOF 5 mg BID (non-responders) or TOF 5 mg BID for 6 months (all) • PBO for 3 months then TOF 10 mg BID (non-responders) or by TOF 10 mg BID for 6 months (all)	Required: MTX; Allowed: prednisone ≤10 mg daily, NSAIDs	ACR50/70, HAQ-DI, DAS28-ESR; other PROs are described in separate study
ORAL Sync	792	Active RA, refractory to cDMARD or bDMARD	• TOF 5 mg BID for 12 months (ACR20:52.1%) • TOF 10 mg BOD for 12 months (ACR20:56.6%) • PBO (ACR20:30.8%) for 6 months, then TOF 5 mg BID or 10 mg BID for 6 months	Required: one cDMARD (no potent immunosuppressives, such as azathioprine or cyclosporin A) Allowed: prednisone <10 mg daily, NSAIDs	ACR 50/70, HAQ-DI, DAS28-ESR, DAS28-CRP

BID, twice daily; BIW, twice weekly; FACIT, Functional Assessment Of Chronic Illness Therapy; PBO, placebo

Schwartz et al. Nat Rev Drug Discov 2017;16:843–862. doi: 10.1038/nrd.2017.201

CSF
Cytokine Signalling Forum

Clinical Trials of Tofacitinib: RA, PsA

Study	N	Participants	Intervention and efficacy	cDMARD	Other outcome measures
Rheumatoid Arthritis					
ORAL Scan	797	Active RA, prior use of bDMARDs or cDMARDs permitted	• TOF 5 mg BID for 12 months (ACR20: 51.5%) • TOF 10 mg BID for 12 months (ACR20: 61.8%) • PBO for 3 months (ACR20: 25.3%) then TOF 5 mg BID (non-responders) or TOF 5 mg BID for 6 months • PBO for 3 months then TOF 10 mg BID (non-responders) or TOF 10 mg BID for 6 months	Required: MTX Allowed: prednisone ≤10 mg daily, NSAIDs	ACR50/70, HAQ-DI, DAS28-ESR, DAS28-CRP, vdH-mTSS, FACIT
ORAL Start	958	Treatment-naïve active RA	• TOF 5 mg BID for 6 months (ACR20: 71.3%) • TOF 10 mg BID for 6 months (ACR20: 76.1%) • MTX up to 20 mg weekly (ACR20: 50.5%)	Allowed: anti-malarials, prednisone <10 mg daily, NSAIDs	ACR50/70, HAQ-DI, DAS28-ESR, DAS28-CRP, vdH-mTSS, FACIT
Psoriatic Arthritis					
OPAL Beyond	395	Active PsA refractory to TNFis	• TOF 5 mg BID (PASI75: 49.6%) • TOF 10 mg BID (PASI75: 47%) • PBO for 3 months (PASI75:71.3%) then TOF 5 or 10 mg BID for 3 months	Required: one cDMARD	ACR 50/70, HAQ-DI, PASI75, DLQI, DSS; 6-month outcomes
OPAL Broaden	422	PsA	• TOF 5 mg BID (PASI75: 50.5%) • TOF 10 mg BID (ACR20: 60.6%) • Adalimumab 40 mg BIW (ACR20: 51.9%) • PBO for 3 months (PASI75:33.3%) then TOF 5 or 10 mg BID for 9 months	Required: one cDMARD	ACR 50/70, HAQ-DI, PASI75, DLQI, DSS; 12-month outcomes
OPAL Balance	817	PsA	• As above	As above	As above

BID, twice daily; BIW, twice weekly; FACIT, Functional Assessment Of Chronic Illness Therapy; PsA, psoriatic arthritis; PASI, Psoriasis Area And Severity Index; PBO, placebo

Schwartz et al. Nat Rev Drug Discov 2017;16:843–862. doi: 10.1038/nrd.2017.201

CSF
Cytokine Signalling Forum

Clinical Trials of Tofacitinib: Psoriasis

Study	N	Participants	Intervention and efficacy	cDMARD	Other Outcome Measures
Psoriasis					
OPT Pivotal 1 and 2	1859	Active plaque psoriasis	• PBO FOR 16 weeks (PASI75: 6.2% and 11.4%, respectively*), then TOF 5 or 10 mg BID • TOF 5 mg (PASI75: 39.9% and 46%, respectively*) • TOF 10 mg (PASI75: 59.2% and 59.6%, respectively*)	None	PGA (clear or almost clear), PASI50/90, DLQI, BSA, NAPSI, 28-week results separate
OPT Compare	1106	Chronic stable active plaque psoriasis	• PBO (PASI75: 5.6%) • Etanercept 50 mg BIW (PASI75: 58.8%) • TOF 5 mg BID (PASI75: 39.5%) • TOF 10 mg BID (PASI75: 63.6%)	None	PGA (clear or almost clear), PASI50/90, BSA, patient-reported itch severity
OPT Retreat-ment	666	Chronic active plaque psoriasis	• TOF 5 mg (PASI75: 49.9%) • TOF 10 mg BID (PASI75: 63.9%) • TOF 5 mg BID for 24 weeks, then withdrawal for 16 weeks (PASI75: 22.9%) • TOF 10 mg BID for 24 weeks, then withdrawal for 16 weeks (PASI75: 18%)	None	PGA (clear or almost clear), PASI50/90, DLQI
OPT Extend	3631	Psoriasis	• As above	None	As above

*For Pivotal 1 and 2 trials, respectively

BID, twice daily; BIW, twice weekly; BSA, body surface area; DLQI, Dermatology Life Quality Index; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area And Severity Index; PBO, placebo; PGA, Physician's Global Assessment

Schwartz et al. Nat Rev Drug Discov 2017;16:843–862. doi: 10.1038/nrd.2017.201

CSF
Cytokine Signalling Forum

Clinical Trials of Tofacitinib: Ulcerative Colitis

Study	N	Participants	Intervention and efficacy	cDMARD	Other outcome measures
Ulcerative colitis					
OCTAVE (Induction 1 and 2)	1139	Moderate-to severely active disease refractory to corticosteroids, cDMARDs or TNFis	• PBO (disease remission: 6.2% and 3.6%, respectively*) • TOF 10 mg BID (disease remission: 18.5% and 16.6%, respectively*)	None	Mucosal healing, clinical response
OCTAVE Sustain	593	PBO or TOF-treated patients with clinical response in OCTAVE Induction 1 or 2	• PBO (disease remission: 11.1%) • TOF 5 mg (disease remission: 34.3%) • TOF 10 mg (disease remission: 40.6%)	None	Mucosal healing, clinical response, sustained clinical responses, sustained steroid-free remission
OCTAVE Open	1732	All patients in OCTAVE Induction and Sustain trials	• As above	None	As above

*For Induction 1 and 2 trials, respectively

BID, twice daily; PBO, placebo

Schwartz et al. Nat Rev Drug Discov 2017;16:843–862. doi: 10.1038/nrd.2017.201

CSF
Cytokine Signalling Forum

Baricitinib

- Baricitinib is a first-generation jakinib that has been studied extensively in patients with RA
  - Inhibits JAK1 and JAK2
  - Not metabolized by cytochrome P450 enzymes
- Approved (EMA) for the treatment of RA
  - In clinical trials, baricitinib outperformed MTX and was superior to adalimumab in patients who were refractory to MTX
- Resubmission of a NDA to the FDA is planned for January 2018 to clarify appropriate doses and safety concerns

EMA, European Medicines Agency; FDA, Food and Drug Administration; JAK, Janus kinase; NDA, new drug application

Schwartz et al. Nat Rev Drug Discov 2017;16:843–862. doi: 10.1038/nrd.2017.201

CSF
Cytokine Signalling Forum

Clinical Trials of Baricitinib: RA

Study	N	Participants	Intervention	Concomitant DMARDs	Study duration	Efficacy (ACR)	Other outcome measures
RA-BEACON	527	Active RA refractory to bDMARDs	• BARI 2 mg daily • BARI 4 mg daily • PBO	Allowed: cDMARDs, NSAIDs, prednisone ≥10 mg daily	24 weeks (outcomes reported at 12 weeks)	PBO: 27% BARI 2 mg: 49% BARI 4 mg: 55%	ACR50/70, HAQ-DI, DAS28-ESR, DAS28-CRP, CDAI, SDAI
RA-BUILD	684	Active RA refractory to bDMARDs (no prior bDMARDs)	• BARI 2 mg daily • BARI 4 mg daily • PBO	Allowed: up to 2 cDMARDs, NSAIDs, prednisone ≥10 mg daily	24 weeks	PBO: 39% BARI 2 mg: 66% BARI 4 mg: 62%	ACR50/70, HAQ-DI, DAS28-ESR, DAS28-CRP, CDAI, SDAI, MJS duration and severity, vdH-mTSS
RA-BEGIN	584	Active RA, DMARD-naïve (≤3 doses of MTX allowed)	• BARI 4 mg daily • MTX • BARI 4 mg daily + MTX	Required: MTX Allowed: NSAIDs, prednisone ≥10 mg daily	52 weeks (outcomes reported at 24 weeks)	MTX: 62% BARI 4 mg: 77% BARI 4 mg + MTX: 78%	ACR50/70, HAQ-DI, DAS28-ESR, DAS28-CRP, CDAI, SDAI, vdH-mTSS
RA-BEAM	1305	Active RA on stable background MTX	• PBO • BARI 4 mg daily • Adalimumab 40 mg BIW	Required: MTX Allowed: NSAIDs, prednisone ≥10 mg daily	24 weeks (outcomes reported at 12 weeks)	PBO: 40% Adalimumab: 61% BARI 4 mg: 70%	ACR50/70, HAQ-DI, DAS28-ESR, DAS28-CRP, CDAI, SDAI, MJS duration and severity, vdH-mTSS

BARI, baricitinib; BIW, twice weekly; MJS, morning joint stiffness; PBO, placebo; vDH-mTSS, van der Heijde modified total Sharp score

Schwartz et al. Nat Rev Drug Discov 2017;16:843–862. doi: 10.1038/nrd.2017.201

CSF
Cytokine Signalling Forum

Other Approved Jakinibs

- Ruxolitinib (JAK1 and JAK2) is approved by the FDA and EMA for the treatment of patients with myeloproliferative neoplasms
- Baricitinib (JAK1, JAK2) is approved by the EMA for the treatment of patients with RA
- Oclacitinib (JAK1) is approved by the FDA for the treatment of canine allergic dermatitis
  - This provides strong precedent for the use of jakinibs to treat atopic dermatitis in humans; a clinical trial of baricitinib for atopic dermatitis is ongoing

EMA, European Medicines Agency; FDA, Food and Drug Administration; JAK, Janus kinase

Schwartz et al. Nat Rev Drug Discov 2017;16:843–862. doi: 10.1038/nrd.2017.201

CSF
Cytokine Signalling Forum

JAK Inhibition – Safety

- Of the first-generation jakinibs, the safety profile of TOF is the best characterized
  - The safety profiles of baricitinib and other first-generation jakinibs are similar to that of TOF
  - AEs reported with first-generation agents include infection, anemia and leukopenia, and gastrointestinal perforation
  - Long-term monitoring is needed to determine how JAK inhibition affects the risk of cardiovascular disease and cancer
- Second generation ‘selective’ jakinibs are in development with the aim of maintaining the efficacy seen with first-generation agents, while improving safety

AE, adverse effects

Schwartz et al. Nat Rev Drug Discov 2017;16:843–862. doi: 10.1038/nrd.2017.201

CSF
Cytokine Signalling Forum

Jakinibs in Clinical Development

Drug	Target	Status	Diseases
Ruxolitinib (INC424)	JAK1, JAK2	Phases 2 and 3 Phases 2 and 3 Phase 2 Phase 2 Phase 2	Various cancers GVHD RA AA Vitiligo, AA, psoriasis, AD (topical)
Tofacitinib (CP690550)	JAK3>JAK1>> (JAK2)	Phase 2 Phase 2	AA, Crohn's disease, ankylosing spondylitis, kidney transplant Psoriasis, AA, AD (topical)
Baricitinib (INCB28050, LY3009104)	JAK1, JAK2	Phase 2	GVHD, giant cell arteritis, diabetic nephropathy
Decernotinib (VX509)	JAK3	Phases 2 and 3	RA
Upadacitinib (ABT494)	JAK1	Phase 3 Phases 2 and 3 Phase 2	RA UC, Crohn's disease AD
Filgotinib (GLPG0634)	JAK1	Phase 3 Phases 2 and 3	RA UC, Crohn's disease

AA, alopecia areata; AD, atopic dermatitis; GVHD, graft-versus-host disease; JAK, Janus kinase; UC, ulcerative colitis

Schwartz et al. Nat Rev Drug Discov 2017;16:843–862. doi: 10.1038/nrd.2017.201

CSF
Cytokine Signalling Forum

Jakinibs in Clinical Development

Drug	Target	Status	Diseases
Itacitinib (INCB39110)	JAK1, JAK2	Phase 2	Psoriasis, RA, pruritus
Peficitinib (ASP015K)	Pan-JAK	Phase 3	RA
R333*	JAK, SYK	Phase 2	Discoid lupus erythematosus
PF-06651600	JAK3	Phase 2	RA, AA, UC
PF-06700841	JAK1, TYK2	Phase 2	Psoriasis, AA, UC
BMS-986165	TYK2	Phase 2	Psoriasis
Solicitinib (GSK2586184, GLG0778)*	JAK 1	Phases 1 and 2	Psoriasis, SLE
PF-04965842*	JAK1	Phase 2	Psoriasis, AD

*Further development discontinued

AA, alopecia areata; AD, atopic dermatitis; JAK, Janus kinase; UC, ulcerative colitis; SLE, systemic lupus erythematosus

Schwartz et al. Nat Rev Drug Discov 2017;16:843–862. doi: 10.1038/nrd.2017.201

CSF
Cytokine Signalling Forum

Jakinibs Under Early Investigation

Drug	Target	Status	Diseases
SAR-20347	JAK1, TYK2	Preclinical	Psoriasis
Cerdulatinib (PRT-062070)	Pan-jakinib, SYK	Preclinical	Collagen-induced arthritis
NDI-031407	TYK2	Preclinical	Inflammatory bowel disease, psoriasis
NDI-031232	TYK2	Preclinical	Response to IL-12
SHR-0302	Pan-jakinib	Phase 1	RA
VR588	Pan-jakinib	Early phase 1	Severe asthma
SB-1578	JAK2, FLT3, c-FMS	Phase 1	Healthy subjects
JTE-052	Non-selective	Phase 1	Atopic dermatitis

JAK, Janus kinase

Schwartz et al. Nat Rev Drug Discov 2017;16:843–862. doi: 10.1038/nrd.2017.201

CSF
Cytokine Signalling Forum

Conclusions

- First generation non-selective jakinibs (e.g. TOF and baricitinib) have demonstrated efficacy and favorable safety profiles in clinical trials and are approved for the treatment of patients with RA
  - Regulatory submissions for other immune-related and inflammatory conditions such as psoriasis, PsA, ulcerative colitis and juvenile idiopathic arthritis are in progress
- A number of second-generation jakinibs are in clinical development
  - These selective agents aim to provide similar efficacy and improved safety profiles compared with first-generation jakinibs
  - Important questions remain about the advantages and limitations of improved JAK selectivity

Schwartz et al. Nat Rev Drug Discov 2017;16:843–862. doi: 10.1038/nrd.2017.201

CSF
Cytokine Signalling Forum