Review

# Selectivity, efficacy and safety of JAKinibs: new evidence for a still evolving story

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# Journal Club 2024/1/9 by Dr.大村

JAK阻害薬の包括的な総説：
　5種類のJAKiの比較

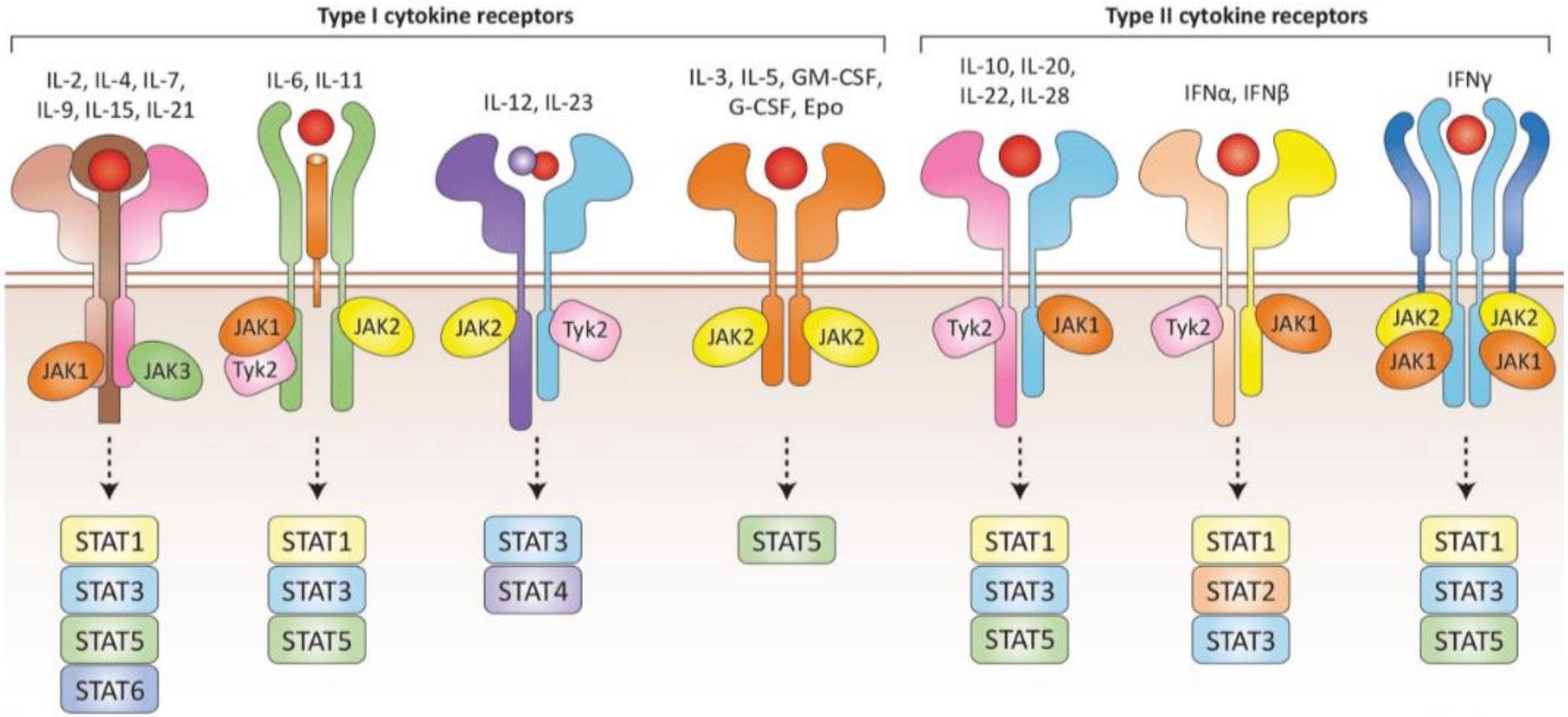



**Figure 1** Type I/II cytokine receptors. Type I/II family cytokines signal through different heteromeric receptors which define the family (box 1). Members of the type I/II cytokine family include interleukins (ILs), interferons (IFNs), IFN-like cytokines, colony-stimulating factors, hormones and growth factors. The combinatorial complexity of cytokine receptor signalling is mediated by specific binding of JAK isoforms to intracellular domains

# JAK/STAT signaling pathwayの基本

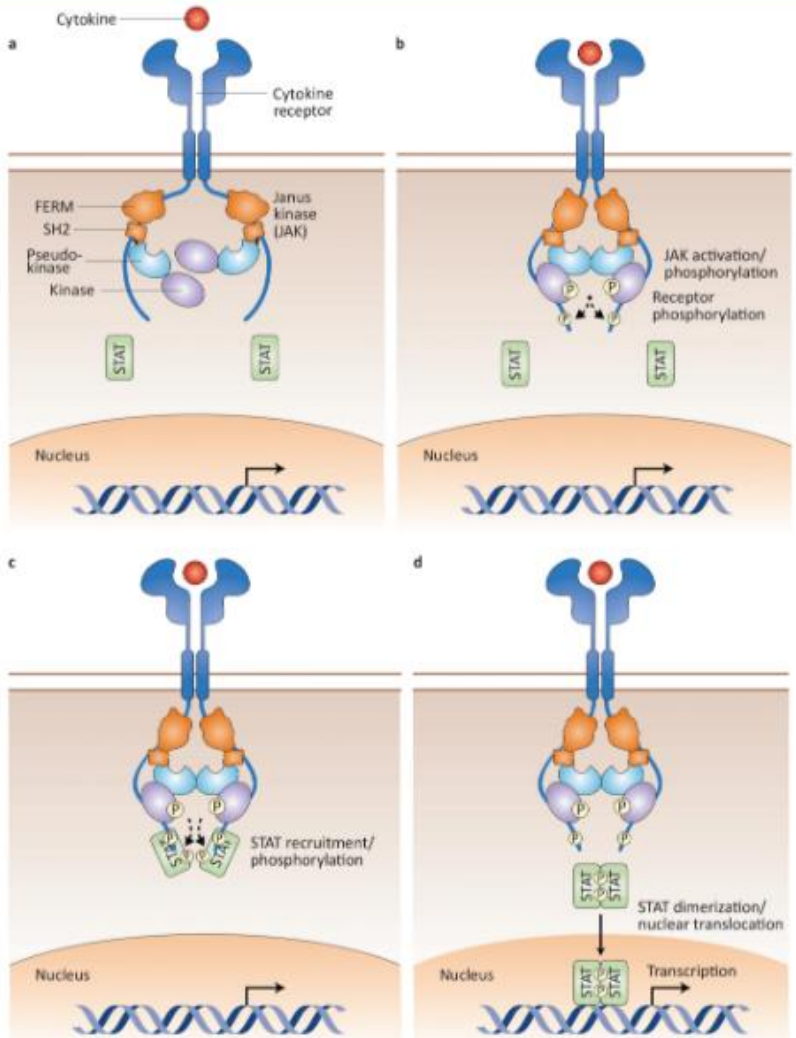


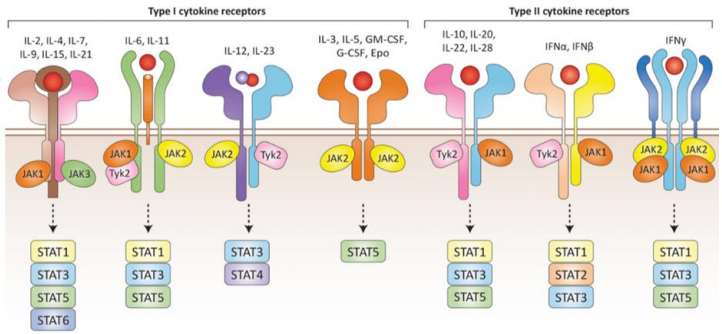

Figure 2 JAK-STAT signalling pathway. (A) Individual JAKs are constitutively associated with their specific receptors through their FERM and SH2 domains. (B) On cytokine engagement, JAKs become activated and phosphorylate each other, as well as the intracellular tails of their receptors. (C) Phosphorylation of the receptor chains generates docking sites for STATs, which can bind to the cytoplasmic domain of the receptor facilitating

# JAK/STAT 変異と疾患

**Table 1** JAKs and STATs with associated phenotypes

| JAK/STAT | Knockout mouse phenotype | Genetic links to human diseases |
|---|---|---|
| JAK1 | Perinatally lethal | GOF: somatic mutations are seen in ALL, AML, solid-organ malignancies |
| JAK2 | Embryonically lethal, absence of erythropoiesis | GOF: PV, PMF, ET, hypercoagulable state, haematological malignancies<br>Polymorphisms: Behçet's disease |
| JAK3 | Defective T and B cell maturation | LOF: T- NK- B+ severe combined immunodeficiency |
| TYK2 | Reduced response to type I interferon and IL-12, defective STAT3 activation | LOF: primary immunodeficiency characterised by dermatitis and impaired antiviral and anti-tb immunity |
| STAT1 | Impaired response to type I and II interferons, susceptibility to viral infections | LOF: primary immunodeficiency with viral susceptibility<br>GOF: chronic mucocutaneous candidiasis, blood cytopenias |
| STAT2 | Impaired response to type I interferon and susceptibility to viral infections | LOF: increased susceptibility to viral mutations |
| STAT3 | Embryonically lethal | LOF: AD-HIES<br>GOF: germline mutations: multisystem auto-immune diseases<br>Somatic mutations: LGL and other T cell lymphomas<br>Polymorphisms: Behçet's disease |
| STAT4 | Impaired Th1 differentiation | Polymorphisms: RA, SLE, Sjögren's syndrome<br>LOF: mycosis |
| STAT5a/STAT5b | Neonatally lethal: few surviving animals at birth are grossly runted and die after a few weeks | Deficiency: autoimmunity, bleeding diathesis, immunodeficiency and dwarfism<br>Somatic mutations: LGL |
| STAT6 | Impaired Th2 differentiation | Polymorphisms: asthma, atopy, increased IgE |

AD, atopic dermatitis; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; ET, essential thrombocythemia; GOF, gain of function; HIES, hyper IgE syndrome; IL, interleukin; JAK, Janus kinase; LGL, leukaemia, large granular lymphocytic leukaemia; LOF, loss of function; PMF, primary myelofibrosis; PV, polycythemia vera; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; STAT, signal transducer and activator of transcription; Th, T helper.



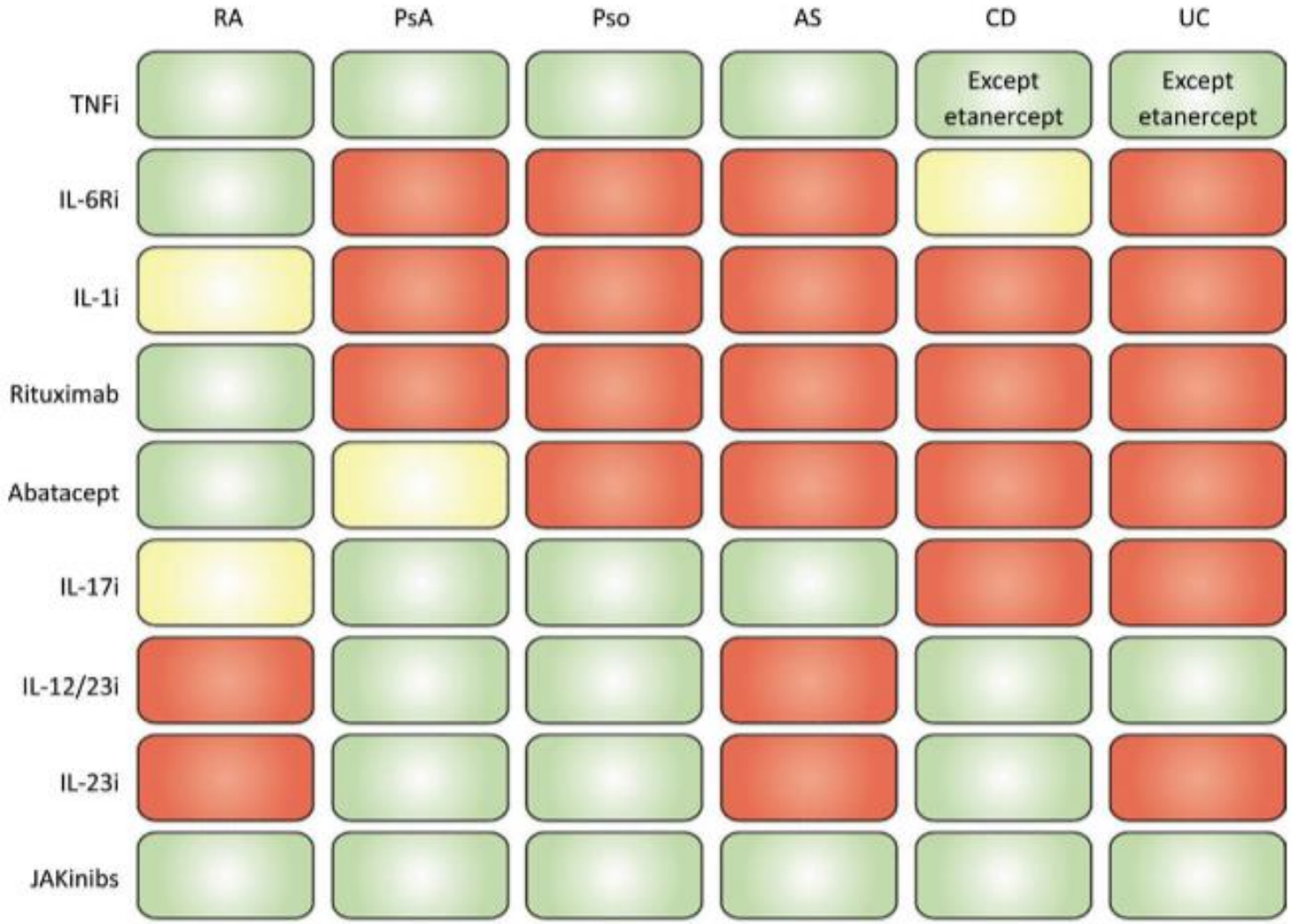

JAK1 LOF mutation =>
再発性抗酸菌感染
膀胱がん
GOF mutation =>
免疫異常、HES
SNV: JIA

JAK2 GOF mutation =>
骨髄増殖性疾患
SNV: ベーチェット病

JAK3 LOF mutation => SCID

Tyk2 SNV: SLE, IBD, 乾癬, MS
SSc, IMM, PBC, TID

# 各疾患に適応承認をもつ薬剤




緑：有効
黄：low efficacy
赤：無効

**Figure 3** Efficacy of various approved agents across different therapies. Green: good efficacy; orange: low efficacy (some not approved for the respective indication); red: no efficacy (not approved for the respective indication). AS, ankylosing spondylitis; CD, Crohn's disease; i, inhibitor(s); IL, interleukin; JAKinibs, Janus kinase inhibitors; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; TNF, tumour necrosis factor; UC, ulcerative colitis.

# In vitroのJAKiの選択性

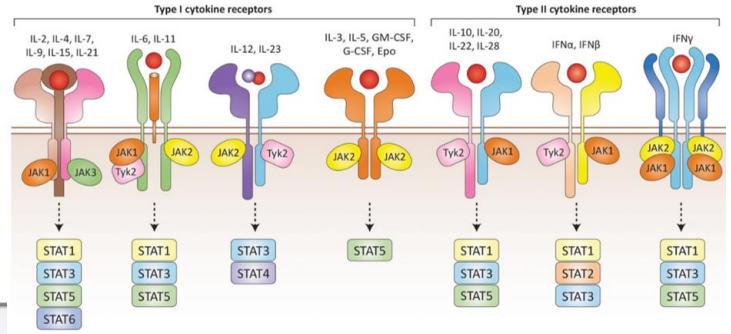



**Table 2** In vitro selectivity of common JAKinibs for the major families of type I/II cytokines

| | | Type I cytokine receptor | | | | Type II cytokine receptor | | |
|---|---|---|---|---|---|---|---|---|
| Receptor family | | GP-130 family | IL-2R CGC family | IL-12/23 family | CβC family | IL-10 family | Type I IFNs | Type II IFNs |
| Cytokine ligands | | IL-6, 11, 27, LIF, OSM | IL-2, 4, 7, 9, 15, 21 | IL-12, 23 | IL-3, IL-5, GM-CSF | IL-10, 19, 20, 22, 26 | IFNα, β | IFNγ |
| Asc JAKs | | JAK1, JAK2, TYK2 | JAK1, JAK3 | JAK2, TYK2 | JAK2 | JAK1, JAK2, TYK2 | JAK1, TYK2 | JAK1, JAK2 |
| Downstream STATs | | STAT1, 3, 5 | STAT1, 3, 5, (6) | STAT3, 4 | STAT5 | STAT1, 3, 5 | STAT1, 2, 3 | STAT1, 3, 5 |
| Inhibitors in increasing order of selectivity | Tofacitinib | +++ | +++ | +++ | +++ | +++ | +++ | +++ |
| | Peficitinib | +++ | +++ | ++ | ++ | +++ | +++ | +++ |
| | Baricitinib | +++ | +++ | +++ | +++ | +++ | +++ | +++ |
| | Upadacitinib | +++ | +++ | ++ | + | +++ | +++ | +++ |
| | Filgotinib | +++ | +++ | + | + | +++ | +++ | +++ |
| | Abrocitinib | +++ | +++ | – | – | +++ | +++ | +++ |

The degree of inhibition is normalised against the ability of each JAKinib to inhibit JAK1 as measured by the $IC_{50}$ value in nM.
+++=$IC_{50}$ of the most inhibited associated JAK for a given cytokine family is lower than or equal to the $IC_{50}$ for JAK1.
++=$IC_{50}$ of the most inhibited associated JAK for a given cytokine family is onefold to twofold higher than the $IC_{50}$ for JAK1.
+=$IC_{50}$ of the most inhibited associated JAK for a given cytokine family is 2-fold to 10-fold higher than the $IC_{50}$ for JAK1.
–=$IC_{50}$ of the most inhibited associated JAK for a given cytokine family is >10 times higher than the $IC_{50}$ for JAK1.
GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; JAK, Janus kinase; STAT, signal transducer and activator of transcription.

# 選択性/非選択性JAKiの副作用

- 重篤な感染症はいずれも上昇
- 帯状疱疹はFilのみ上昇なし
- 好中球減少はFilのみなし
- Hb低下はTofaなし、FilはHb上昇
- PltはTofa↑、Bari↑、Upa↓、Fil↓
- VTEはtofa↑、Bari↑、他は↔(?)
- CreはFilのみ不変、他は↑
  （ただしこれはBK virus-associated nephropathyによるもので腎移植でTofa vs CyAの結果や自己炎症でのBariのデータ）
- すべてのJAKiでCPK↑とあるが、詳細不明
- 悪性腫瘍はTofa↑、他は↔(?)

| JAK | | | Infections | | Hematologic | | Liver and GIT | Thrombosis | Lipids | Others | Malignancies |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Serious | URT | NEU | LYM | TA | VTE | HDL | CREA | Malignancies |
| | | | OI | HZ | Hb | PLT | GIP | PE | LDL | CPK | NMSC |
| Non-selective | Tofacitinib | JAK1-3 | ↑ | ↑ | ↓ | ↑ | ↑ | ↑* | ↑ | ↑ | ↑* |
| | | | ↑ | ↑↑ | ↔ | ↑ | ↔(?) | ↑* | ↑ | ↑ | ↔(?) |
| | Peficitinib | JAK1-3 | ↑ | ↑ | ↓ | ↓ | ↑ | ↔(?) | ↑ | ↑ | ↔(?) |
| | | | ↑ | ↑↑ | ↓ | ↔ | ↔(?) | ↔(?) | ↑ | ↑ | ↔(?) |
| | Baricitinib | JAK1,2 | ↑ | ↑ | ↓ | ↔ | ↑ | ↑ | ↑ | ↑ | ↔(?) |
| | | | ↑ | ↑↑ | ↓ | ↑ | ↔(?) | ↑(?) | ↑ | ↑ | ↔(?) |
| Selective | Upadacitinib | JAK1,2 | ↑ | ↑ | ↓ | ↓ | ↑ | ↔(?) | ↑ | ↑ | ↔(?) |
| | | | ↑ | ↑↑ | ↓ | ↓ | ↔(?) | ↔(?) | ↑ | ↑ | ↔(?) |
| | Filgotinib | JAK1 | ↑ | ↑ | ↔ | ↔ | ↔ | ↔(?) | ↑ | ↔ | ↔(?) |
| | | | ↑ | ↔ | ↑ | ↓ | ↔(?) | ↔(?) | ↑ | ↑ | ↔(?) |

**Figure 5** Side effects of selective versus non-selective JAKinibs. *In patients with cardiovascular or VTE risk factors at baseline. Arrows indicate the respective adverse event risk compared with placebo treatment with an slightly (↑), highly (↑↑), lower (↓) or similar (↔) risk. Question marks in brackets highlight areas of uncertainty, especially for safety events that need exploration in large observational studies. JAK, Janus kinase; HZ, herpes zoster; CREA, creatinine; URT, upper respiratory tract; NEU, neutrophils; LYM, lymphocytes; Hb, haemoglobin; PLT, platelets; TA, transaminases; GIT, gastrointestinal tract; GIP, gastrointestinal perforations; VTE, venous thromboembolism; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CPK, creatine phosphokinase; NMSC, non-melanoma skin cancer; OI, opportunistic infection.

# 各JAKiの様々な疾患に対する有効性と適応承認状況

| Drug/JAK | | | Comparator (versus) / State of investigation | Rheumatoid arthritis | Psoriatic arthritis | Ankylosing spondylitis | Chronic plaque psoriasis | Ulcerative colitis | Crohn's disease | Atopic dermatitis | Systemic lupus erythm |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Non-selective | Tofacitinib | JAK1-3 | versus PLC | | | | | | | (topical) | |
| | | | versus TNF(R)i | ADA (NI) | ADA | | ETN (NI) | | | | |
| | | | State | Approved | Approved | Approved | Phase III[e] | Approved | Phase II | Phase II | Phase I[e] |
| | Peficitinib | JAK1-3 | versus PLC | | | | | | | | |
| | | | versus TNF(R)i | | | | | | | | |
| | | | State | Appr. (JPN) | | | Phase II | Phase II | | | |
| | Baricitinib | JAK1,2 | versus PLC | | | | 8/10 mg[b] | | | | |
| | | | versus TNF(R)i | ADA (S) | | | | | | | |
| | | | State | Approved | | | Phase II | | | Approved | Phase III |
| Selective | Upadacitinib | JAK1,2 | versus PLC | | | | | | | | |
| | | | versus TNF(R)i | ADA (S) | ADA (NI/S) | | | | | | |
| | | | State | Approved | Approved | Approved | | Approved | Approved | Approved | Phase II[d] |
| | Filgotinib | JAK1 | versus PLC | | | | | | | | |
| | | | versus TNF(R)i | ADA (NI) | | | | | | | |
| | | | State | Appr. (EU) | Phase II | Phase II | | Approved | Phase II | | |

**Figure 4** Admission of approved selective versus non-selective JAKinibs. The label in the upper box indicates the comparator referenced with the colour code (green colour indicates significant differences; red colour indicates no significant difference; yellow indicates mixed results; blue colour indicates studies meeting non-inferiority; purple indicates no formal statistical comparison and numerically similar results. *No formal statistical comparison, numerically similar results. †Tofacitinib is currently not pursued for drug approval for plaque psoriasis. ‡8/10 mg reached statistical significance, no significance was observed for 2/4 mg versus placebo. §One trial, safety only (NCT02535689). ¶Phase II trial, no data/results published (NCT03978520). **No difference was observed in patients with small bowel CD,[158] ADA, adalimumab; ETN, etanercept; JAK, Janus Kinase; NI, non-inferiority; PLC, placebo; S, superiority; TNF(R)i, tumour necrosis factor alpha receptor inhibitor.

# JAKi外用薬の開発状況

円形脱毛症、アトピー性皮膚炎湿疹、感染などに外用薬の開発が進んでいる

**Table 3** Clinical developmental stages of topical JAKinibs for skin diseases

| Disease | JAKi | Target | Route | Phase of development | Trial identifier |
|---|---|---|---|---|---|
| Alopecia areata | Ruxolitinib | JAK1/JAK2 | Topical | Phase II | NCT02553330 |
| | Tofacitinib | JAK1/JAK3 | Topical | Phase II | NCT02812342 |
| | Ifidancitinib | JAK1/JAK3 | Topical | Phase II | NCT03759340 |
| Atopic dermatitis | Ruxolitinib | JAK1/JAK2 | Topical | Phase III | NCT03745651 |
| | | | Topical | Phase III | NCT03745638 |
| | | | Topical | Phase I (paediatric) | NCT03257644 |
| | | | Topical | Phase I | NCT03920852 |
| | Delgocitinib | Pan-JAK | Topical | Phase II | NCT03725722 |
| | | | Topical | Phase I | NCT03826901 |
| | Tofacitinib | JAK1/JAK3 | Topical | Phase II | NCT02001181 |
| | Brepocitinib | JAK1/TYK2 | Topical | Phase II | NCT03903822 |
| | Ifidancitinib | JAK1/JAK3 | Topical | Phase II | NCT03585296 |
| Chronic hand eczema | Delgocitinib | Pan-JAK | Topical | Phase III | NCT04871711 |
| | | | Topical | Phase III | NCT05355818 |
| | | | Topical | Phase II | NCT02664805 |
| Cutaneous GVHD | Ruxolitinib | JAK1/JAK2 | Topical | Phase II | NCT03395340 |
| | | | Topical | Phase II | NCT03954236 |
| Discoid lupus erythematosus | Delgocitinib | Pan-JAK | Topical | Phase II | NCT03958955 |
| Healthy | PF-06263726 | Pan-JAK | Topical | Phase I | NCT01981681 |
| Hidradenitis suppurativa | Ruxolitinib | JAK1/JAK2 | Topical | Phase II | NCT04414514 |
| Lichen planus | Ruxolitinib | JAK1/JAK2 | Topical | Phase II | NCT03697460 |
| Necrobiosis lipoidica | Ruxolitinib | JAK1/JAK2 | Topical | Phase II | NCT04492618 |
| Psoriasis | Ruxolitinib | JAK1/JAK2 | Topical | Phase II | NCT00820950 |
| | | | Topical | Phase II | NCT00617994 |
| | | | Topical | Phase II | NCT00778700 |
| | Tofacitinib | JAK1/JAK3 | Topical | Phase II | NCT01831466 |
| | | | Topical | Phase II | NCT01246583 |
| | | | Topical | Phase II | NCT00678561 |
| | | | Topical | Phase I | NCT02193815 |
| | PF-06700841 | JAK1/TYK2 | Topical | Phase II | NCT03850483 |
| Vitiligo | Ruxolitinib | JAK1/JAK2 | Topical | Phase III | NCT04057573 |
| | | | Topical | Phase III | NCT04052425 |
| | | | Topical | Phase III | NCT04530344 |
| | | | Topical | Phase II | NCT02809976 |
| | | | Topical | Phase II | NCT03099304 |

GVHD, graft-versus-host disease; JAK, Janus kinase; JAKinibs, JAK-inhibitors.

# （参考）
# JAKi選択性解析

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**BRIEF REPORT**

## Differences in JAK Isoform Selectivity Among Different Typ of JAK Inhibitors Evaluated for Rheumatic Diseases Throu In Vitro Profiling

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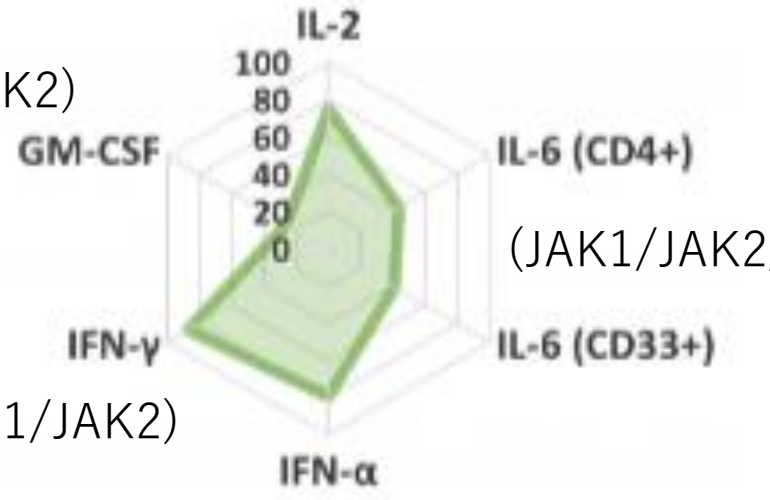
(JAK1/JAK3)

(JAK2)




(JAK1/JAK2/Tyk2)

(JAK1/JAK2)

(JAK1/Tyk2)

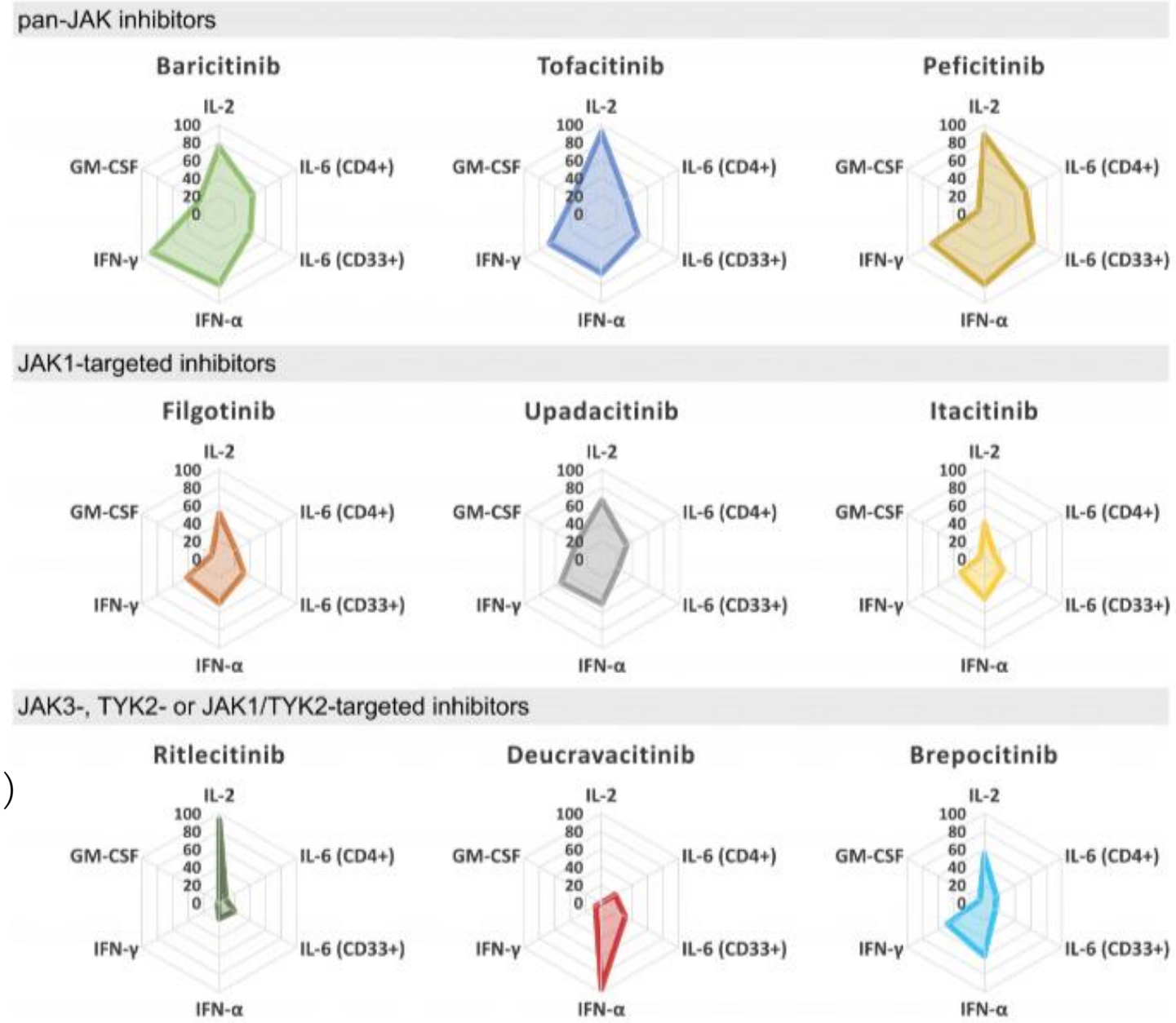



**Figure 1.** Cytokine inhibition profiles of JAK inhibitors (Jakinibs) in immune cells from patients with rheumatoid arthritis (RA). The indicated inhi-