studies of mice seeded with a single bacterial species. Even so, metabolomic shifts could potentially have pathogenetic effects that might not always be attributable to a single microbial species, as different taxa might have coordinated functions in driving specific pathogenic metagenomic pathways in an individual's gut community. To develop practical therapeutic approaches, we need to consider how to move beyond simple taxon transplantation to the in situ stabilization of communities that reinforce immune homeostasis and oppose dysregulated inflammatory responses[10].

Gregg J. Silverman

The Laboratory of B cell immunobiology and the Division of Rheumatology, NYU School of Medicine, New York, NY, USA.

e-mail: gregg.silverman@nyumc.org

https://doi.org/10.1038/s41584-018-0152-z

1. Bengtsson, A. A. & Ronnblom, L. Role of interferons in SLE. *Best Pract. Res. Clin. Rheumatol.* **31**, 415–428 (2017).
2. Manfredo Vieira, S. et al. Translocation of a gut pathobiont drives autoimmunity in mice and humans. *Science* **359**, 1156–1161 (2018).
3. Chen, Y. et al. Microbial symbionts regulate the primary Ig repertoire. *J. Exp. Med.* **215**, 1397–1415 (2018).
4. Greiling, T. M. et al. Commensal orthologs of the human autoantigen Ro60 as triggers of autoimmunity in lupus. *Sci. Transl Med.* **10**, eaan2306 (2018).
5. Rosenbaum, J. T. & Silverman, G. J. The microbiome and systemic lupus erythematosus. *N. Engl. J. Med.* **378**, 2236–2237 (2018).
6. Morgan, X. C. et al. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. *Genome Biol.* **13**, R79 (2012).
7. van der Meulen, T. A. et al. Shared gut, but distinct oral microbiota composition in primary Sjogren's syndrome and systemic lupus erythematosus. *J. Autoimmun.* https://doi.org/10.1016/j.jaut.2018.10.009 (2018).
8. Silverman, G. J. et al. Lupus nephritis is linked to immunity to an intestinal commensal lachnospiraceae species [abstract]. *Arthritis Rheumatol.* **69** (Suppl. 10), 1786 (2018).
9. Silverman, G. J. et al. Identification of a gut pathobiont immunostimulatory lipoglycan antigen linked to lupus nephritis [abstract]. *Arthritis Rheumatol.* **70** (Suppl. 10), 104 (2018).
10. Taroncher-Oldenburg, G. et al. Translating microbiome futures. *Nat. Biotechnol.* **36**, 1037–1042 (2018).

Acknowledgements
The author declares that he is supported by grants from the NIH and the Judith and Stewart Colton Autoimmunity Center.

Competing interests
The author declares no competing interests.

THERAPY IN 2018

Selective Janus kinase inhibitors come of age

John J. O'Shea and Massimo Gadina

Janus kinase (JAK) inhibitors (jakinibs) that target downstream signalling by a large range of cytokines are effective in treating autoimmune and rheumatic diseases. Newer jakinibs that selectively inhibit individual JAKs and a narrower spectrum of cytokines have now been developed, but how do these inhibitors compare with existing drugs?

Inappropriate and excessive production of cytokines is a cornerstone of our present understanding of inflammatory and autoimmune pathology. Accordingly, the development of biologic therapeutics that target individual cytokines has revolutionized the treatment of these diseases. Still, many patients do not achieve complete remission, calling for alternative strategies such as the development of Janus kinase (JAK) inhibitors (jakinibs). Two first-generation pan-jakinibs have been approved by both the FDA and the European Medicines Agency (EMA): tofacitinib (which targets JAK1, JAK2 and JAK3) for rheumatoid arthritis (RA), psoriatic arthritis and ulcerative colitis; and baricitinib (which targets JAK1 and JAK2) for RA (FIG. 1). However, in 2018, results from clinical trials of two next-generation JAK1-selective inhibitors were published with positive results in psoriatic arthritis[1], ankylosing spondyloarthritis[2] and RA[3,4]. The question arises: how do these next-generation jakinibs compare with first-generation agents from the perspective of efficacy and safety?

JAKs are phosphotransferases that bind to the intracellular domains of cytokine receptors and transmit signals to activate immune responses. The family of cytokines that signal via JAKs includes many interleukins, interferons, colony stimulating factors and hormone-like cytokines (such as erythropoietin). The receptors for these cytokines signal via various combinations of four JAKs (JAK1, JAK2, JAK3 and TYK2). First-generation jakinibs, such as tofacitinib and baricitinib (and oclacitinib in dogs), block more than one JAK, and thereby can inhibit a large number of cytokines; these and other pan-jakinibs are being investigated as therapeutic agents for a wide variety of autoimmune diseases[5]. Common adverse effects include infection, anaemia, neutropenia, lymphopenia and hyperlipidaemia. These effects are expected owing to the inhibition of multiple JAKs and many cytokines[5,6], and the rate of infections in patients treated with these drugs is similar to the rate with other immunosuppressive drugs and biologic agents. Venous thromboembolism occurred in clinical trials of baricitinib at a rate of ~5 events per 1000 patient-years, but whether this rate is significantly different from the background rate is not yet clear. Although the risk–benefit profile of jakinibs has been judged to be acceptable by regulatory agencies, new jakinibs that inhibit the function of fewer cytokines with greater specificity might have fewer adverse effects.

In 2018, two phase III trials of upadacitinib (a selective JAK1 inhibitor) for RA successfully achieved primary end points of 20% improvement in ACR criteria (ACR20) and a 28-joint disease activity score using C-reactive protein (DAS28-CRP) of ≤3.2 at 12 weeks[3,4]. However, a reduction of haemoglobin levels occurred in some of the patients in the SELECT-BEYOND study, particularly at high doses of upadacitinib (grade 3 or 4 reduction in 7.9% of patients receiving 30 mg). Anaemia after treatment with first-generation jakinibs is generally assumed to be due to inhibition of JAK2 and erythropoietin signalling[5]. Anaemia after upadacitinib therapy might therefore indicate that upadicitinib also inhibits JAK2, especially at high doses. Generally though, the magnitude of anaemia does not seem to be a major limitation in the use of tofacitinib, baricitinib or upadacitinib. Notably, 4 of 329 patients treated with upadacitinib in the SELECT-BEYOND trial had pulmonary thromboembolism, but whether the rate of this complication is substantially different from the background rate in RA is not clear, and neither is an underlying mechanism for this effect.

In 2018, two phase II trials of another JAK1-selective inhibitor, filgotinib, showed efficacy in patients with psoriatic arthritis[1]

Key advances

- Filgotinib, a JAK1-selective inhibitor, demonstrates efficacy in psoriatic arthritis with no unexpected safety signals[1].
- Filgotinib is efficacious in patients with ankylosing spondylitis who did not respond to nonsteroidal anti-inflammatory drugs[2].
- Two phase III trials demonstrate efficacy of upadacitinib, a selective JAK1, in RA[3,4].

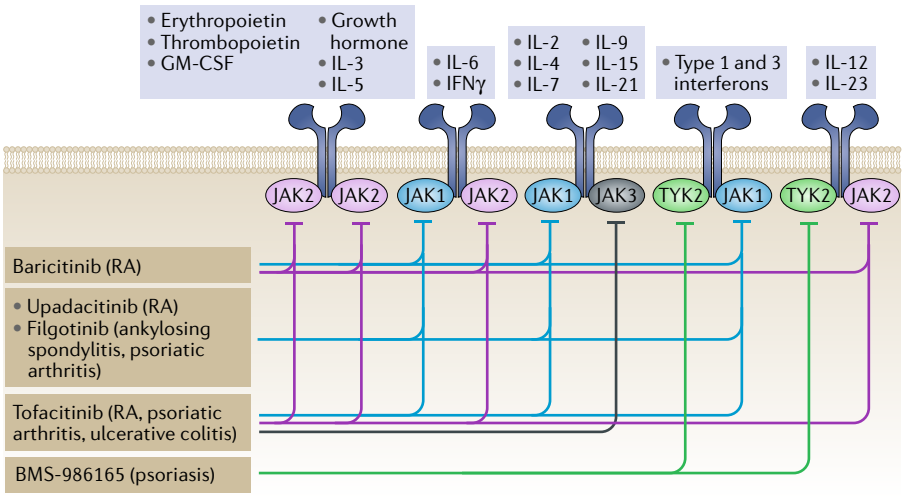

Fig. 1 | **Selectivity of JAK inhibitors.** Different cytokine receptors signal via different Janus kinases (JAKs). First-generation JAK inhibitors affect a broad spectrum of cytokines, whereas selective JAK inhibitors have the potential to limit the activity of a much smaller subset of cytokines and thereby enable signalling via other JAK-dependent pathways to be maintained and, potentially, reduce the incidence of adverse effects. GM-CSF, granulocyte–macrophage colony stimulating factor; RA, rheumatoid arthritis.

and in patients with ankylosing spondylitis[2]. Unlike the upadacitinib trials[3,4], filgotinib treatment resulted in a mean positive change in haemoglobin (6 g/l compared with 1 g/l for placebo) and platelet count (−16 giga/l for filgotinib versus 7 giga/l for placebo)[3]. Increase in serum lipid levels occurs with all jakinibs; however, filgotinib was associated with a favourable shift in the HDL:LDL ratio[1,2]. Whether these distinctions between upadacitinib and filgotinib (effects on haemoglobin and lipids) are a matter of dose-dependent inhibition of JAK1 itself, of kinases other than JAK1 or of some other factor is not clear. Long-term extension studies and real-life experience with these drugs will hopefully shed light on the true benefit of JAK1 selectivity in the management of arthritis and other autoimmune disorders.

Cytokines of the IL-12/IL-23 family as well as type I and type III interferons are dependent on the activity of TYK2, and jakinibs targeting TYK2 are also being developed for diseases ranging from systemic lupus erythematosus to psoriasis. BMS-986165 is the most advanced of the TYK2-selective jakinibs, and positive results of a 12-week randomized, double-blind, placebo-controlled phase II trial of this inhibitor with 287 patients with psoriasis have been published[7]. Unlike other jakinibs that target the kinase domain of the JAK, BMS-986165 binds to the kinase-like domain, potentially enabling an even greater degree of selectivity. The primary end point of the study[7], a 75% reduction in the Psoriasis Area and Severity Index (PASI) score (PASI 75), was achieved in a substantial proportion of patients receiving ≥3 mg daily with 25% of patients treated with the highest dose (12 mg daily) having a PASI score of 100. Rates of response were similar to previous studies of adalimumab (a TNF inhibitor) or ustekinumab (an IL-12/IL-23 inhibitor). Some adverse effects common to first-generation jakinibs, such as cytopenias or hyperlidaemia, did not occur, but infections, acne and one case of melanoma were recorded.

Together, these trials[1–4,7] support the hypothesis that improved JAK selectivity is not only possible but is also efficacious for psoriatic arthritis, ankylosing spondylitis, RA and psoriasis. Although more data are required, selective jakinibs do not necessarily reduce the risk of infection compared with first-generation jakinibs. One means of potentially reducing adverse effects is to avoid systemic JAK inhibition. For example, an exciting development has been the development of a new inhaled jakinib that has efficacy in a preclinical model of asthma[8]. Furthermore, to limit systemic exposure, existing and new topical jakinibs are being tested for a variety of dermatological disorders[5].

Nevertheless, effective therapy for many severe autoimmune diseases can require the use of combination therapy and multiple immunomodulatory drugs. Only case reports combining jakinibs with biologic agents have so far been presented[9], but this option is an important strategy to explore further; rigorous clinical trials using both biologic agents and jakinibs in some combination will of course be needed to establish safety and efficacy. The demonstration of the efficacy of next-generation selective jakinibs is clearly an important development, but there will probably be more instalments in the jakinib story as we seek the best therapeutic strategies to further the treatment of rheumatic and autoimmune diseases with these versatile drugs.

John J. O'Shea[1] ** and Massimo Gadina*[2]

[1]*Molecular Immunology and Inflammation Branch, National Institutes of Arthritis and Musculoskeletal and Skin diseases, Bethesda, MD, USA.*

[2]*Translational Immunology Section, National Institutes of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD, USA.*

**e-mail: john.oshea@nih.gov*

https://doi.org/10.1038/s41584-018-0155-9

1. Mease, P. et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial. *Lancet* **392**, 2367–2377 (2018).
2. van der Heijde, D. et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebo-controlled, phase 2 trial. *Lancet* **392**, 2378–2387 (2018).
3. Burmester, G. R. et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* **391**, 2503–2512 (2018).
4. Genovese, M. C. et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet* **391**, 2513–2524 (2018).
5. Gadina, M. et al. Translational and clinical advances in JAK-STAT biology: the present and future of jakinibs. *J. Leukoc. Biol.* **104**, 499–514 (2018).
6. Winthrop, K. L. The emerging safety profile of JAK inhibitors in rheumatic disease. *Nat. Rev. Rheumatol.* **13**, 234–243 (2017).
7. Papp, K. et al. Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis. *N. Engl. J. Med.* **379**, 1313–1321 (2018).
8. Dengler, H. S. et al. Lung-restricted inhibition of Janus kinase 1 is effective in rodent models of asthma. *Sci. Transl. Med.* **10**, eaao2151 (2018).
9. Barroso, N. S., Miller, E. Z. & Furst, D. E. A case series on patients on tofacitinib in combination with a biologic. *J. Clin. Rheumatol.* **24**, 349–351 (2018).

Competing interests

J.J.O'S. declares that he and the NIH hold a patent related to JAK inhibition in autoimmune disease and receive royalties from this patent. Both authors declare that they have a Collaborative Research and Development Agreement related to JAK inhibitors with Pfizer.