Review

TYK2 inhibition and its potential in the treatment of chronic inflammatory immune diseases

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Summary

Immune-mediated chronic inflammatory diseases have emerged as a leading cause of morbidity and mortality in Western countries over the last decades. Although multiple putative factors have been suspected to be causally related to the diseases, their overarching etiology remains unknown.

This review article summarizes the current state of scientific knowledge and understanding of the role of non-receptor tyrosine kinases, with a special focus on the Janus kinase TYK2 in autoimmune and immune mediated diseases as well as on the clinical properties of its inhibition.

A panel of experts in the field discussed the scientific evidence and molecular rationale for TYK2 inhibition and its clinical application. Reviewing this meeting, we aim at providing an integrated overview of the clinical profile of TYK2 inhibition and its potential in targeted pharmacological therapy of chronic autoimmune and immune-mediated diseases, with a special focus on inflammatory diseases of the skin.

Introduction: Need for new therapeutic principles and dosage forms for inflammatory diseases

Chronic immune-mediated inflammatory diseases such as psoriasis, psoriatic arthritis, axial and peripheral spondyloarthritis as well as inflammatory bowel diseases have an estimated prevalence of 5–7 % in Western society [1]. They are associated with increased morbidity and mortality and have a significant impact on patients' quality of life (QoL). However, research into the pathogenesis of immune-mediated inflammatory diseases allows for the identification of immunological factors, and thus for the development of effective therapies.

Successful therapies have been developed that target inflammatory cytokines of type 2, such as interleukin (IL)-4 and IL-13 in atopic diseases, or type 1/type 3 such as IL-12 and IL-23 that contribute to the pathogenesis of autoimmune and chronic inflammatory diseases, including psoriasis and rheumatoid arthritis (Figure 1). Cytokines are released by immune cells that belong to the innate and the specific immune system. They exert pro-inflammatory or anti-inflammatory effects and are involved in the control of cellular functions, particularly inflammatory reactions. Immune cells often respond to cytokines by secreting cytokines themselves, triggering a "cytokine cascade". Additionally, non-immune cells may also respond to, and secrete, cytokines. The various pro- and anti-inflammatory processes of the immune system are characterized by distinctive cytokine profiles [2].

Under physiological conditions, cytokines are produced only temporarily in response to a corresponding stimulus and are subsequently degraded very rapidly. In chronic inflammatory diseases, on the other hand, constitutively elevated levels of cytokines are found in the affected tissues [3, 4].

One example of an autoimmune disease is psoriasis for which many therapeutic options have been developed in recent years. Due to its chronic, sometimes severe inflammatory nature that can last for decades, psoriasis has a negative impact on the patients' quality of life. Even though novel therapies have the potential to tremendously improve the patients' condition, treatment continues to be a challenge for some dermatologists [5].

Patients with moderate to severe disease are candidates for systemic therapy. Beside conventional systemic anti-psoriatic drugs like fumaric acid esters (FAE), methotrexate (MTX), ciclosporin (CsA) or retinoids, selective biological therapies have been developed to target specific cytokines. Factors that are biologically and therapeutically relevant in patients with psoriasis are tumor necrosis factor (TNF), IL-17, and IL-23 [6]. Hence, many systemic treatment options exist for patients with psoriasis and PsA that are safe and effective. However, biologicals have to be administered by injections and many patients prefer oral therapeutics [7].

Due to its chronic nature that may last for decades, the development of additional psoriasis therapies is needed that are safe and effective in the long term.

Furthermore, there is an unmet need for disease-modifying drugs with a different mechanism of action not only
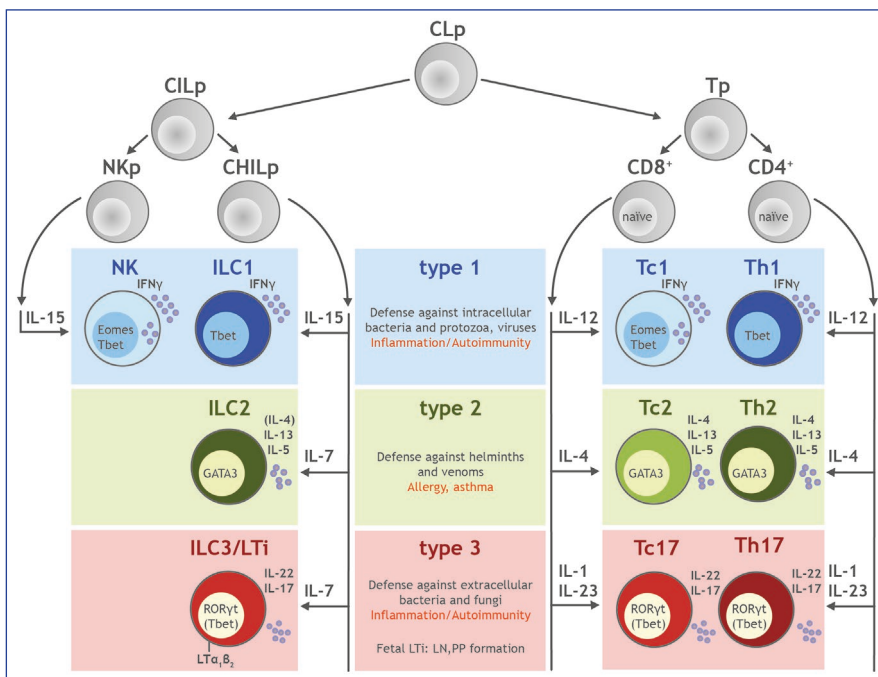
Figure 1 Inflammatory types and involved cytokines. Adapted according to [2].
Abbr.: CILp, Common innate lymphoid precursor; CLp, common lymphoid precursor; Eomes, Eomesodermin; IFN, interferon; IL, interleukin; IL-7R, IL-7 receptor; ILC, Innate lymphoid cell; LN, lymph node; LTi, lymphoid tissue inducer; NK, Natural killer; NKp, Natural killer progenitor PB: Peripheral blood, PP, Peyer patch; ROR, Retinoic acid-related orphan receptor; T-bet, T-box expressed in T cells; Tc, T cell; Th, T-helper cell; Tp, T-cell progenitor.

in psoriasis but also in other autoimmune inflammatory diseases [8].

The Role of TYK2 in the pathogenesis of chronic inflammation and autoimmune diseases

Tyrosine kinases represent a family with about 100 different molecules in the human body. In contrast to transmembrane receptors kinases (such as the epidermal growth factor receptor), non-receptor tyrosine kinases (TYKs) are intracellular enzymes that mediate signal transduction downstream of various cell surface receptors, including cytokine receptors. In chronic inflammatory skin diseases, deregulated signaling of immune cells depending on TYKs have been identified as a major pathogenic component to drive diverse inflammatory processes.

Non-receptor TYKs are associated with various cell surface receptors. They mediate the transduction of extracellular signals to intracellular signalling pathways and cellular effector functions. The Janus kinase (JAK) family is one of the ten classified mammalian non-receptor tyrosine kinase families. It has four members: JAK1, JAK2, JAK3 and TYK2 [9].

Various cytokine receptors engage different pairs of JAK enzymes including TYK2 for the initiation of downstream signaling: Ligand binding promotes JAK activation, leading to the recruitment of various signal transducer and activator of transcription (STAT) factors. Upon phosphorylation by JAKs, STAT molecules translocate to the nucleus. They act as transcriptional activators and repressors and contribute to epigenetic regulations. Due to their key role in cytokine signalling, the JAK family kinases are crucial for maintaining immune homeostasis (Figure 2) [9].

The selective activation of different JAK family kinases determines the spectrum of the mediated biological effects, with TYK2 acting as a pivotal mediator in the immunopathogenesis of chronic inflammatory immune diseases. TYK2 represents an outlier in this family, which in contrast to the JAK molecules does not have an SH2 domain [10]. Importantly, genome wide association studies showed that variants in the TYK2 gene locus are highly associated with the risk of developing psoriasis, Crohn's disease or other chronic inflammatory disorders [11, 12]. Moreover, TYK2 alleles that give rise to a functionally hypoactive protein are statistically protective for various autoimmune pathologies in population samples [13].

Within the chronically inflamed skin in psoriasis, activated dendritic cells release IL-23, which binds to cytokine receptors on CD4+ T cells, induces TYK2/JAK2 and subsequently activates STAT3 [14]. Through the intracellular TYK2/JAK2-STAT3-mediated signaling cascade, preactivated CD4+ T cells differentiate – via the T-cell receptor in the presence of further cytokine signals (such as IL-6, IL-1β and/or TGF-β) – to mature or pathogenic T helper 17 cells (Th17) [15]. Interleukin-23 is also important for the production of
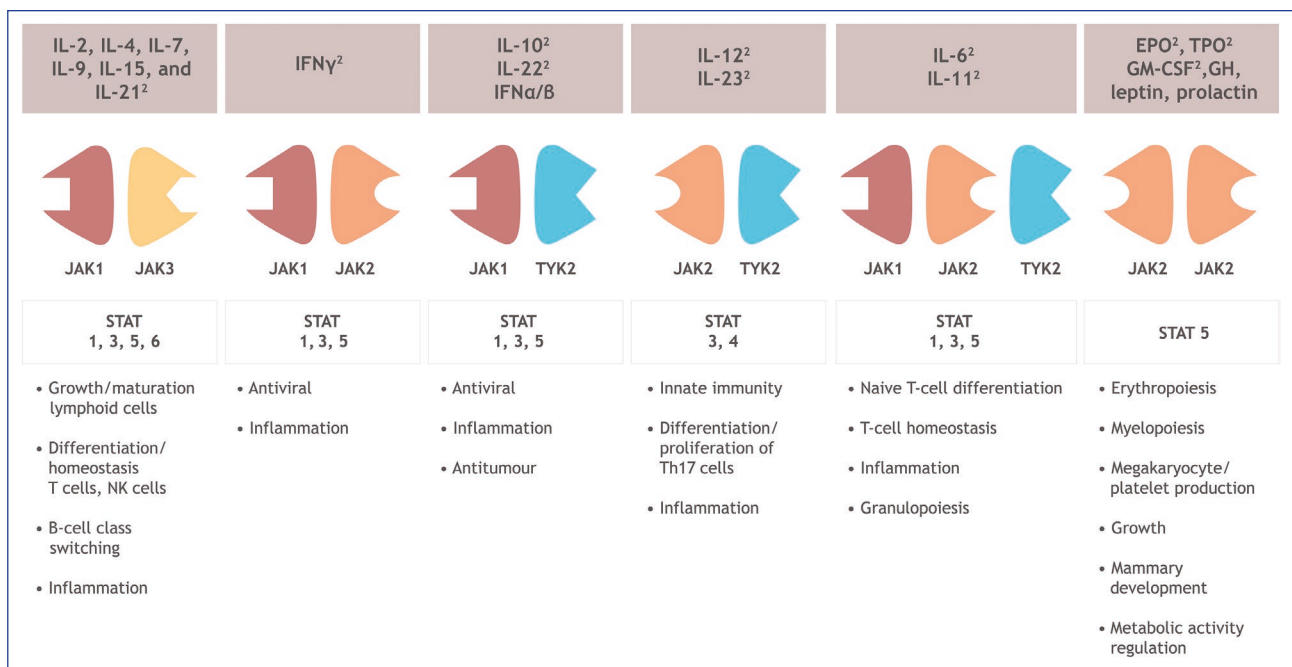
Figure 2 Multiple cytokines signal through JAKs and TYK2. Adapted according to [9] (© Bristol Myers Squibb 2021).
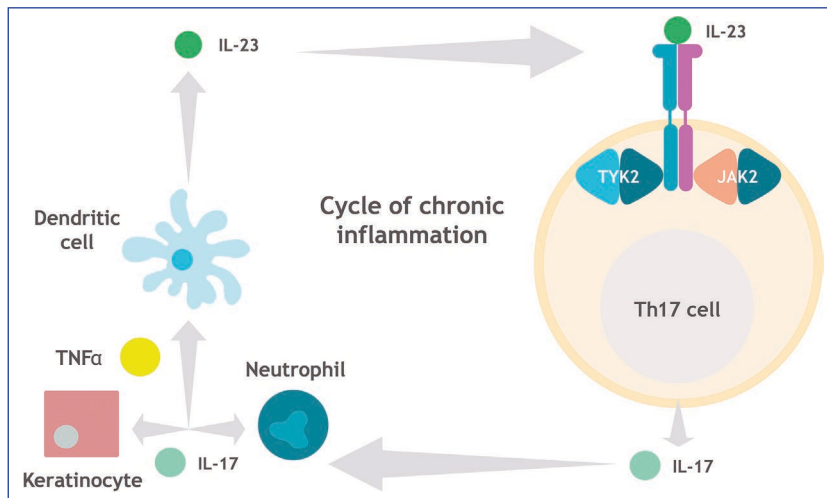
Figure 3 TYK2 signaling in the IL-23/Th-17 axis is important for sustaining psoriasis [17–19] (© Bristol Myers Squibb 2021).

proinflammatory cytokines such as IL-17 and IL-22 by activated IL-23 receptor expressing CD4+ T cells and other immune cells [16]. The secretion of IL-17 and other cytokines by Th17 cells activates keratinocytes and neutrophils, leading to a feedforward loop with resumed activation of dendritic cells and eventually further production of pro-inflammatory cytokines (Figure 3) [17–19].

Based on the aforementioned pathomechanism of Th17/IL-23-mediated inflammation, in addition to the direct neutralization of the cytokine IL-23 by anti-IL-23 antibodies, inhibition of the IL-23 receptor signaling pathway by small molecule inhibitors seems to be feasible. Efficacy and safety of such kinase inhibitors is currently under investigation in clinical studies [20–22].

TYK2 inhibition in plaque type psoriasis – phase II efficacy and safety data and outlook on phase III

The inhibition of tyrosine kinases has been identified as a potential therapeutic option for the targeted treatment of various inflammatory conditions.

Approved JAK inhibitors bind to the ATP binding site of JAKs. High structural homology between the binding sites of the individual JAKs hampers the development of highly selective inhibitors that inhibit only one JAK [23]. However, it is important to avoid such unintentional interference with similar signalling pathways to minimize potential toxicities. It is therefore desirable to achieve better selectivity for the binding sites within the kinase domain [24, 25]. Accordingly, the mechanistic approach for deucravacitinib (BMS-986165) is different from that of approved JAK inhibitors. It specifically binds to the regulatory domain (pseudokinase) of

TYK2, thereby maintaining TYK2 in an inactive conformation and preventing its activation.

Pre-clinical *in vitro* studies have shown that TYK2-mediated signal transduction in T lymphocytes can be blocked [26], with hardly any effect on JAK1, JAK2 and JAK3 signalling.

Deucravacitinib is an oral small molecule TYK2 inhibitor. In contrast to JAK1–3 inhibitors, which target the ATP binding sites, deucravacitinib, via binding to the regulatory domain, selectively blocks IL-23, IL-12 and type I-IFN-mediated signaling, but does not block cytokine reactions mediated by other kinases (such as IL-6, hematopoietic growth factors and the γc-receptor family). Therefore, deucravacitinib can be considered highly selective, which probably contributes to an improved safety profile. The results of the first-in-human phase I study with 108 participants supported this assumption, since no serious adverse events occurred. The study therefore resulted in the further testing of deucravacitinib in diseases such as psoriasis [27].

In a multi-center, randomized, double-blind, placebo-controlled, parallel group phase II dose-finding study involving 267 patients with moderate to severe psoriasis, deucravacitinib was clinically effective at a daily dose of 3 mg and higher (ClinicalTrials.gov identifier NCT02931838).

At week 12, the percentage of patients with a 75 % or greater reduction in the PASI score was statistically significantly higher in patients receiving deucravacitinib (at 3 mg daily or twice daily, at 6 mg twice daily and at 12 mg daily) compared to the placebo group ($P < 0.001$ vs. placebo) (Figure 4) [28].

The most common adverse events were nasopharyngitis, headache, diarrhea, nausea and upper respiratory tract infection. These events occurred slightly more often in patients receiving deucravacitinib compared to the placebo group (deucravacitinib: 55–80 %, placebo: 51 %).
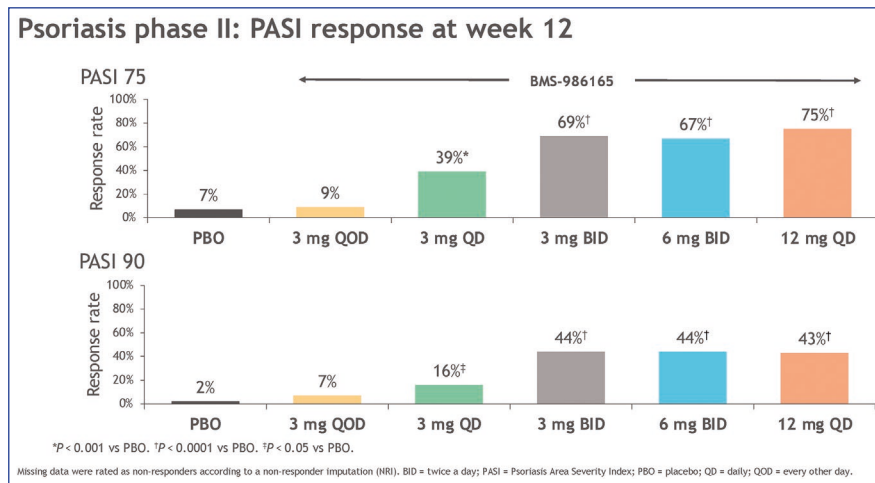
Figure 4 Psoriasis phase II trial data: PASI 75 and PASI 90 response at week 12. Adapted according to [28] (© Bristol Myers Squibb 2021). *$P < 0.001$ vs. PBO. †$P < 0.0001$ vs. PBO. ‡$P < 0.05$ vs. PBO. Missing data were rated as non-responders according to a non-responder imputation (NRI). *Abbr.*: BID, twice a day; PASI, Psoriasis Area Severity Index; PBO, placebo; QD, daily; QOD, every other day.

None of the serious adverse events reported in the active drug group was assessed as being drug-related [28]. Currently, the compound is in phase III trials for psoriasis [28].

Unlike the small molecule inhibitors of JAK1–3 and TYK2, that are less selective among different JAK family members than expected [22, 29], the novel mechanism of action of deucravacitinib involves the specific inhibition of TYK2 only, by binding to its pseudokinase domain without affecting JAK1–3. Specific inhibition of signaling pathways crucially involved in chronic inflammatory conditions may explain the good safety profile of deucravacitinib in the phase II trial. Typically, the safety profile associated with JAK 1–3 inhibitors includes infections and changes in laboratory values [30], such as neutrophil number, hemoglobin levels, HDL levels, and serum creatinine levels. These values are not affected by deucravacitinib [28]. Furthermore, no cases of varicella zoster infections and thromboembolic events, risks associated with JAK 1–3 inhibitors [31, 32], were reported in the phase II trial with deucravacitinib [28].

Outlook: Other potential indications under investigation for TYK2 inhibition

Psoriatic arthritis

Approximately 25 % of patients with psoriasis develop psoriatic arthritis (PsA) within 5–10 years [33]. As plaque psoriasis and PsA share common pathogenic mechanisms, with evidence for T cells playing a key role in the immunopathology [34], TYK2 inhibition presents an attractive target also for the treatment of PsA [35].

TYK2 mediates the signaling of IL-23, IL-12, and type I-IFN-driven responses, leading to the activation of IL-17 secreting Th17 cells. IL-17 is an inflammatory cytokine that stimulates the proliferation and activation of keratinocytes

and synovial fibroblasts [36, 37]. These IL-17-stimulated synovial fibroblasts then express IL-23, which activates the TYK2 pathway leading to a positive feedback loop resulting in chronic inflammation of joint tissues associated with bone and cartilage damage. The pathologic process represents a self-perpetuating activation cycle involving various pro-inflammatory cytokines, such as IL-23, IL-17, IL-1β, and TNF in the synovium of PsA patients [38] (Figure 5). These cytokines play a pivotal role in the disturbed bone homeostasis by networking between the skeletal and immune systems, acting as potent osteoclastogenic cytokines, which induce osteoclast differentiation [39].

Cytokine signaling pathways (IL-23, IFNα, IFNβ) involved in the pathophysiology of PsA are selectively inhibited by deucravacitinib [40]. Currently, the novel small molecule is being investigated in a multi-center, randomized, placebo-controlled, double-blind phase II study in 180 patients with PsA (ClinicalTrials.gov identifier NCT03881059) [40].

Axial spondyloarthritis

Axial spondyloarthritis (axSpA) is a chronic, inflammatory rheumatic disease affecting the axial skeleton, predominantly involving the sacroiliac joints and/or spine [41]. Chronic inflammation, followed by sequential bone erosion and new bone formation characterize the natural disease course. Patients suffer from severe pain, stiffness and fatigue, with the risk of developing fused joints in the sacroiliac area or spinal column in late-stage disease [42].

The underlying pathomechanism of SpA is a systemic overactivity of type 3 immunity, which is supported by IL-23 through the upregulation of IL-17 and IL-22 in lymphocytes [34].

However, the mechanisms underlying SpA pathogenesis have not been completely understood (Figure 6) [43].
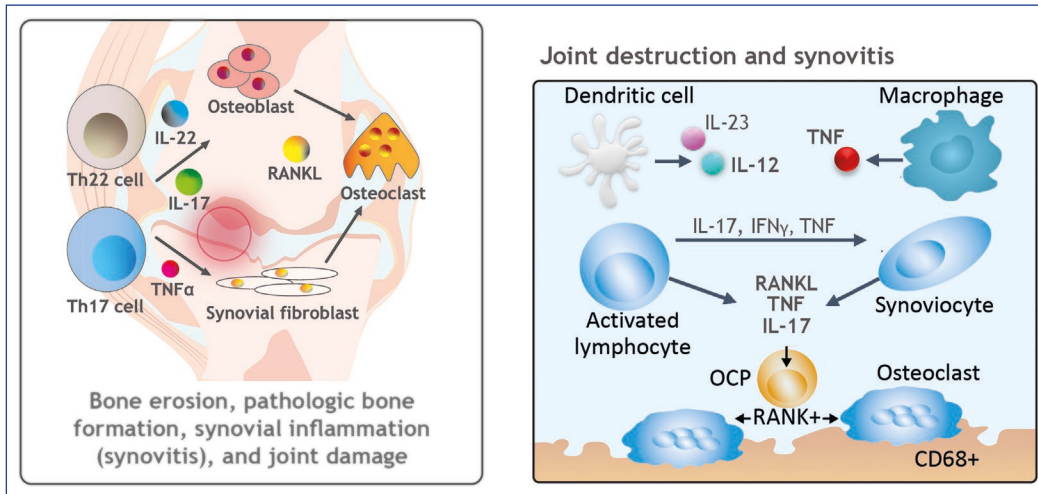
Figure 5 Immuno-pathogenesis of Psoriatic Arthritis (PsA). Adapted according to [40]. *Abbr.:* IFN, interferon; IL, interleukin; OCP, osteoclast precursor; RANK, receptor activator of nuclear factor kappa-B; RANKL, receptor activator of nuclear factor kappa-B ligand; TNF, tumor necrosis factor.

In an IL-23 and Th17-dependent mouse model of SpA, an oral TYK2 inhibitor (NDI-031407) demonstrated promising results as it reduced type 3 immunity and modified disease progression [42].

Postmortem, micro-computed tomography revealed the absence of erosions in the axial and peripheral skeleton in mice treated with the highest dose of NDI-031407. Magnetic resonance imaging of the sacroiliac joint demonstrated
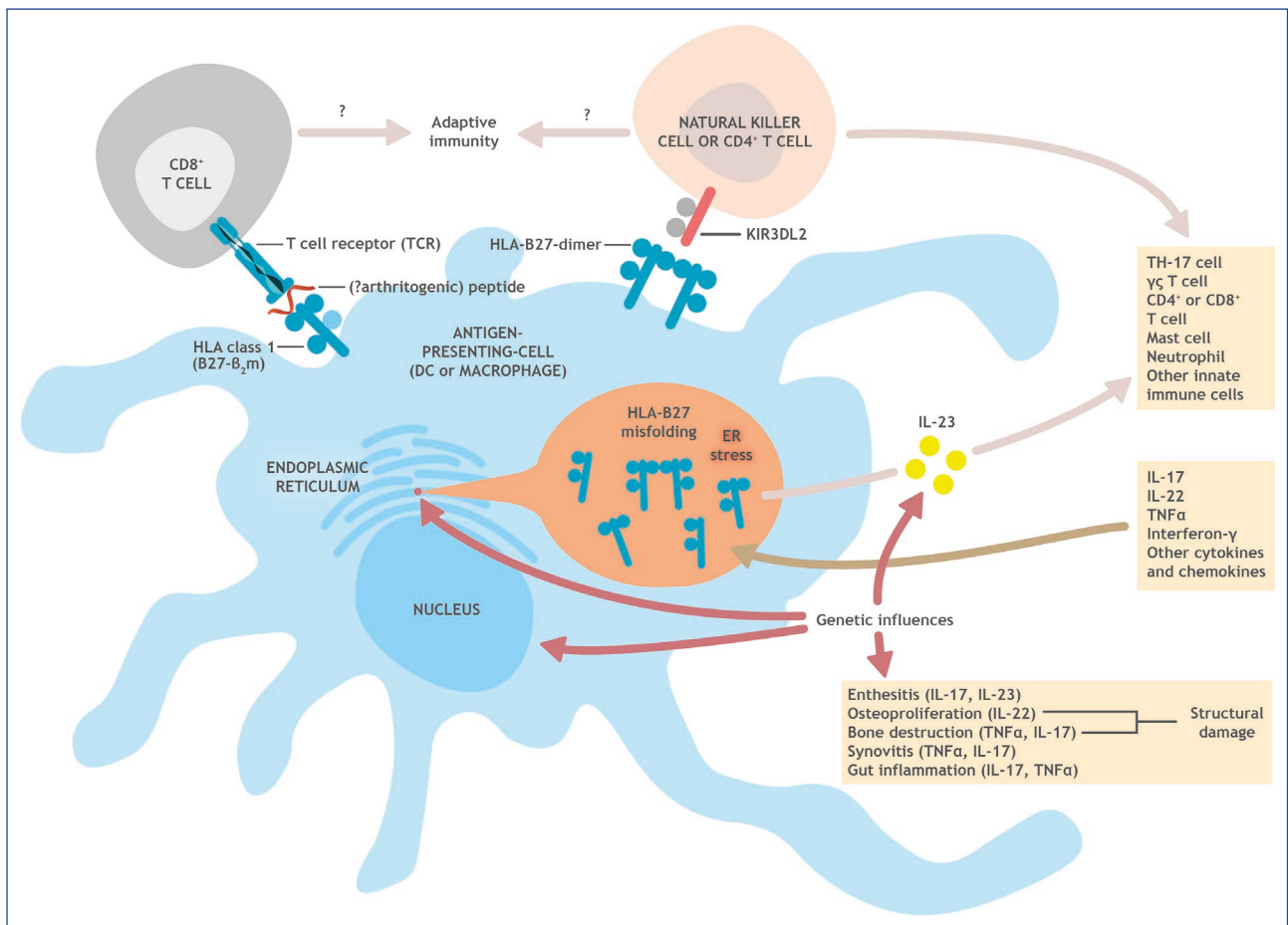
Figure 6 Immunopathogenesis of axial Spondyloarthritis (axSpA). Adapted according to [43].
Abbr.: KIR3DL2, killer cell immunoglobulin-like receptor 3DL2; ER, endoplasmic reticulum; HLA, human leukocyte antigen.
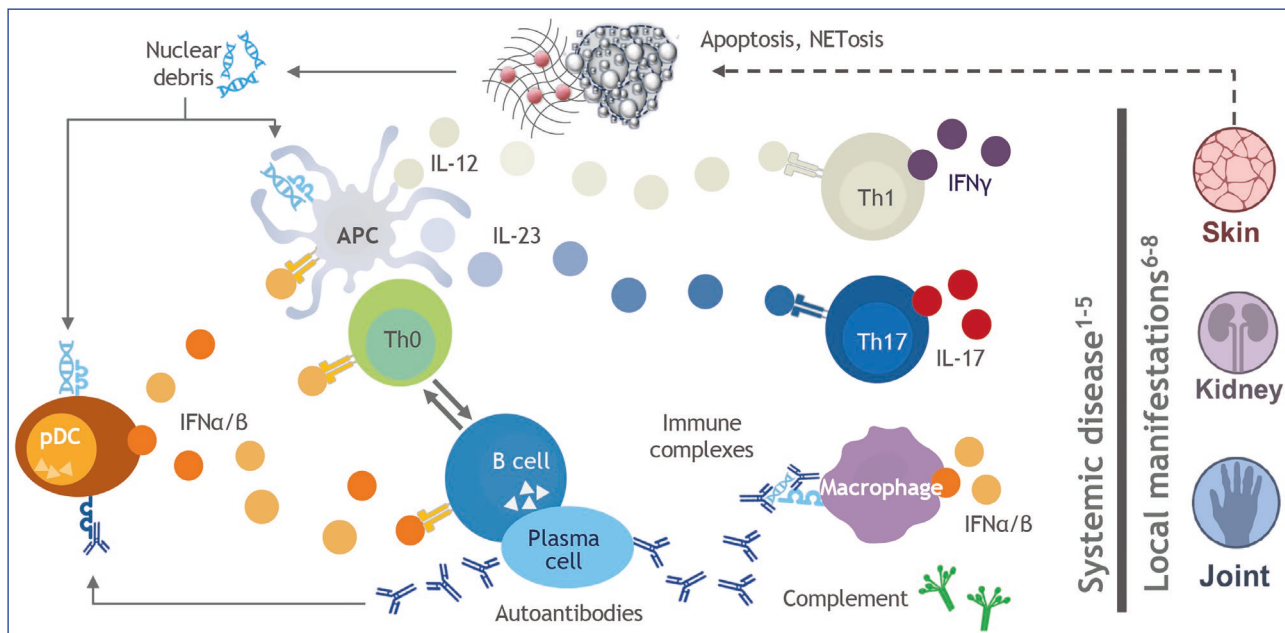
Figure 7 Pathogenesis of Lupus. Multiple cell types and cytokines contribute to the development and chronicity of lupus and its manifestations (© Bristol Myers Squibb 2021).
Abbr.: APC, antigen presenting cell; BCR, B-cell receptor; CD4/40(L), cluster of differentiation 4/40 (ligand); CTLA, cytotoxic T-lymphocyte-associated; pDC, plasmacytoid dendritic cell; TLR, toll-like receptor. 1. Crow MK. J Immunol 2014; 192: 5459–68. 2. Yap DY, Lai KN. J Biomed Biotechnol 2010; 2010: 365083. 3. Larosa M et al. Exp Biol Med 2019; 244: 42–51. 4. Tsokos GC et al. Nat Rev Rheumatol 2016; 12: 716–30. 5. Zharkova O et al. Rheumatol 2017; 56: i55–i66. 6. Wenzel J. Nat Rev Rheumatol 2019; 15: 519–32. 7. Yu F, et al. Nat Rev Nephrol 2017; 13: 483–95. 8. Mahmoud K et al. Curr Opin Rheumatol 2017; 29: 486–92.

disease progression by joint space narrowing and bone marrow edema, which was prevented by TYK2 inhibition [42].

The results were confirmed by histopathology. They show that TYK2 plays an immunomodulatory and pathogenic role in an axSpA model. Furthermore, TYK2 inhibition effectively blocks inflammation and structural changes in this model. For patients with axSpA, TYK2-selective inhibition may be a disease-modifying approach for prevention of post-inflammatory structural changes in the axial skeleton [41, 42]. However, anti-IL-23 antibodies seem to be less effective in PsA phenotypes of SpA.

Systemic lupus erythematosus and lupus nephritis

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a chronic inflammatory response leading to a distinctive facial red rash (malar or butterfly rash), painful and swollen joints, fever, chest pain, hair loss, mouth ulcers, swollen lymph nodes and fatigue. It may be accompanied by kidney inflammation, known as lupus nephritis (LN). Immunologically, it is characterized by imbalanced regulation of Th1, Th2, and Th17 cells with increased plasma levels

of IL-6, IL-10, IL-12, IL-17, IFNγ, IFNα, and decreased levels of IL-4 [44] (Figure 7). In patients with exacerbated SLE, IL-17 is overexpressed and the Th17 subpopulation is increased, which contributes to tissue injury and organ damage [45].

The activated cytokine signaling pattern implies that patients with SLE could benefit from JAK inhibitors, such as small molecules that inhibit signaling of TYK2. In addition to signaling via IL-12 family receptors (IL-12R and IL-23R), TYK2 mediates signaling through the type I-IFN receptor, and IL-10 family receptors (IL-10R and IL-22R) [41]. Blocking TYK2 and its downstream signaling decreases development of Th17 cells followed by reduced secretion of IL-17.

Deucravacitinib is currently being investigated in two phase II trials involving lupus patients: The PAISLEY-SLE Study (ClinicalTrials.gov identifier NCT03252587) is a randomized, double-blind, multi-center, placebo-controlled study evaluating the long-term safety and efficacy of deucravacitinib in patients with SLE. The primary endpoint is the SLE Responder Index 4 (SRI-4) response rate at Week 32. The PAISLEY-LN Study (ClinicalTrials.gov identifier NCT03943147) is also conducted as a randomized,
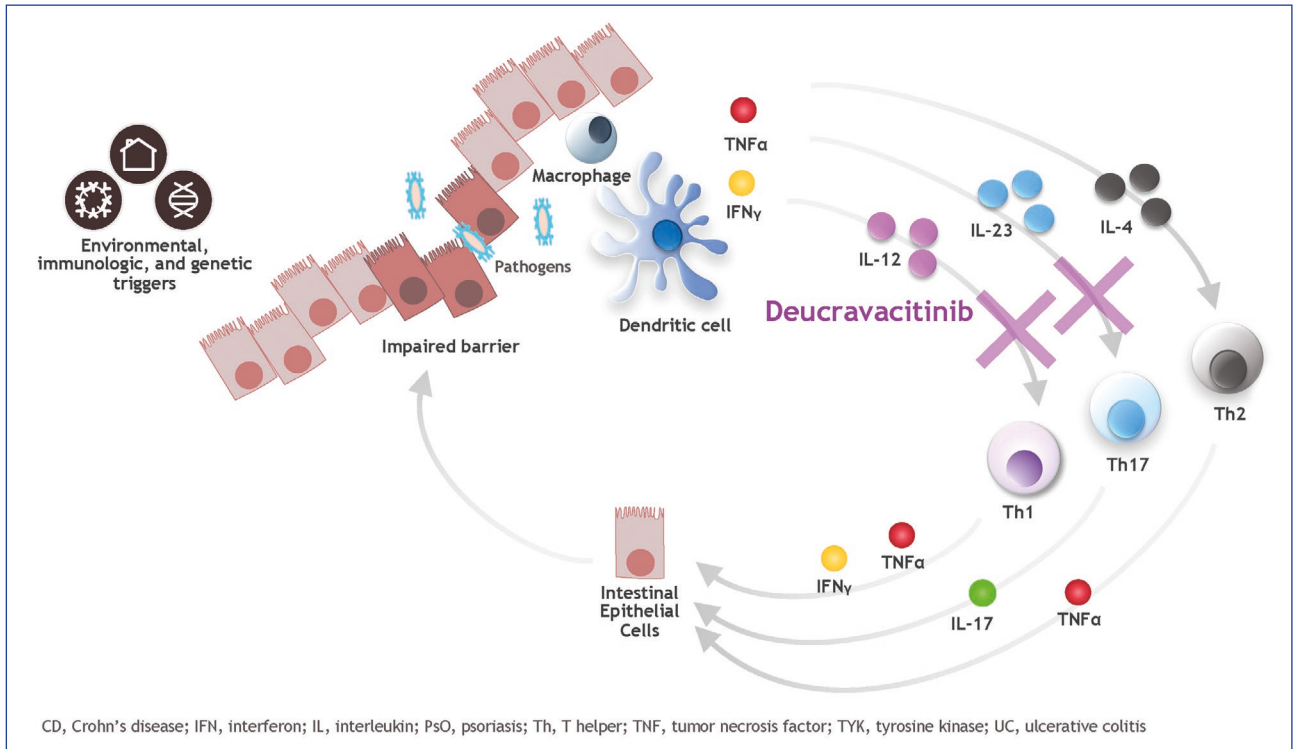
Figure 8 Action of deucravacitinib in inflammatory bowel diseases (IBD) pathogenesis. Adapted according to [55, 56] (© Bristol Myers Squibb 2021).
 Abbr.: CD, Crohn's disease; PsO, psoriasis; TYK, tyrosine kinase; UC, ulcerative colitis.

double-blind, multi-center, and placebo-controlled trial that investigates the efficacy and safety of deucravacitinib in patients with lupus nephritis with a special focus on kidney function.

Inflammatory bowel diseases

Inflammatory bowel diseases (IBD) are chronic disorders of the gastrointestinal tract, the two major forms of which are Crohn's disease (CD) and ulcerative colitis (UC). Symptoms associated with IBD include abdominal pain, (bloody) diarrhea, and numerous extraintestinal manifestations. Long-standing inflammation in both UC and CD is associated with an increased risk of colorectal cancer [46, 47].

While the etiology of IBD is unknown, both CD and UC are characterized by dysregulated host immune responses against components of the intestinal microbiota [48, 49]. Both active UC and CD are characterized by increased mucosal cytokine levels and the targeting of several IBD-associated cytokines has demonstrated efficacy in the treatment of IBD. Monoclonal antibodies directed against TNF were the first biologicals approved for the treatment of IBD [50]. Work in recent years further revealed a central role of IL-12 and IL-23 in intestinal inflammation and showed that

therapeutic blockade of this axis can ameliorate intestinal inflammation in IBD [51]. However, only a subset of IBD patients shows a primary response to available anti-cytokine biologics and a significant proportion of responders develops a secondary loss of response. Mechanism of primary non-response or secondary loss of response include, among others, antigenicity of biological therapy and loss of therapeutic antibodies through an inflamed "leaky gut" [52]. Small molecules targeting TYK2 may potentially address several of these limitations through combined inhibition of several pathogenic cytokines such as IL-12 and IL-23, lack of immunogenicity and limited regulation by enteric protein loss (Figure 8). Consistent with this notion, deucravacitinib demonstrated efficacy in the inhibition of intestinal inflammation in two murine models of IBD [53, 54]. Moreover, the clinical efficacy of deucravacitinib is currently being evaluated in phase II trials in CD and UC [55, 56]. Of note, therapies targeting IL-17 signaling are currently not being pursued in the treatment of IBD or in psoriasis patients with IBD as a comorbid disease, since IL-17 also has a protective effect on the intestinal mucosa. Deucravacitinib influences IL-17. However, since it interferes with upstream IL-23 signaling, TYK2 inhibition has the potential to be as well tolerated as anti-IL-12/23 antibodies in IBD.

Discoid lupus erythematosus, other potential indications and topical therapy

Discoid lupus erythematosus (DLE) and dermatomyositis (DM) are inflammatory autoimmune diseases. Their primary manifestation is the skin, but systemic complications occur. Interface dermatitis with vacuolar degeneration of the basal cell layer and necrotic keratinocytes are characteristic features of the histopathology. Evidence supports that the Th1 cell immune response and specifically the IFN-stimulated JAK-STAT signaling pathway within keratinocytes is involved in their destruction, common to both DLE and DM. In skin samples of patients with DLE and DM, plasmacytoid dendritic cells (pDCs) have been shown to be elevated. They produce higher levels of type I IFNs (IFNα and IFNβ) and initiate the inflammatory cascade observed in skin lesions [57].

JAK inhibitors have great potential for the treatment of these diseases by reducing Th1 proliferation, the production of multiple cytokines and suppressing inflammation. As oral formulations, they are associated with rapid efficacy onset and decreased dependence on corticosteroids [58].

Beside systemic therapies, topical therapy forms are the cornerstone of treatment for some severe inflammatory skin diseases. Topical formulations might be highly beneficial for affected patients, as the side effects, which we know from long-term local steroid application, are unlikely to occur with topical JAK inhibitors. In a study using human diseased skin, strong expression of activated pSTAT2 and pSTAT3 was observed, while no signs of STAT1 activation were seen [59]. Furthermore, IL-17 and IL-22 producing CD4+ T cells are elevated in DLE skin lesions [60]. Therefore, TYK2 inhibition might also be eligible for a topical treatment approach, as TYK2 is involved in the signal transduction of many cytokines, including the regulation of IL-17 expression and the signal transduction of IL-22, via the STAT3 pathway [21, 22].

Conclusions

Inhibition of TYK2 by deucravacitinib is a promising treatment option for psoriasis and other chronic inflammatory autoimmune diseases. Assuming that the specificity of deucravacitinib for TYK2 is associated with limited toxicities compared to JAK1–3 inhibition, and that the efficacy data from phase II trials will be confirmed in phase III, selective TYK2 inhibition may be an alternative immunotherapeutic oral drug compared to first generation biological immunotherapeutics. Dermatologists, rheumatologists and gastroenterologists eagerly follow the efficacy and safety data on the ongoing study program on deucravacitinib. From an immunological point of view, selective TYK2 inhibition is mechanistically an elegant way to interfere with chronic IL-23/Th-17 and/or IFN/Th1-dominated inflammation.

Disclosure

The authors vouch for the content of this publication and confirm that recommendations made by consensus match their viewpoints. Based on chapter-wise contributions of the coauthors, the corresponding author and the last author prepared the initial draft of the manuscript with editorial and writing assistance.

All authors made essential contributions to the conception of the article and drafted one or several paragraphs and/or chapters, revised the content of the manuscript critically, agreed on final approval of the version and agreed on accountability for all aspects of the work.

Conflict of interest
KG received fees for lectures and/or consultancy and grants as investigator from AbbVie, Almirall, Biogen IDEC, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen-Cilag, Leo Pharma, Medac, MSD Sharp & Dohme, Novartis, Pfizer, Roche and UCB.

MA served as a consultant and/or paid speaker for and/or has received research grants and/or honoraria for consulting and/or scientific lectures for and/or received travel expense reimbursement and/or participated in clinical trials sponsored by companies that manufacture drugs used for treatment of psoriasis including AbbVie, Almirall, Amgen, Biogen (Biogen Idec), Boehringer Ingelheim, Celgene, Centocor, Eli Lilly and Company, Janssen-Cilag, LEO Pharma, Medac, MSD (formerly Essex, Schering-Plough), Mundipharma, Novartis, Pfizer, (formerly Wyeth), Pohl Boskamp, Sandoz, and XenoPort.

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