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How to treat a patient with psoriatic arthritis and chronic lymphocytic leukemia?

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Abstract

A 76-year-old male patient who has been suffering from psoriatic arthritis (PsA) for 15 years was diagnosed with chronic lymphocytic leukemia (CLL) 18 months ago. He has been treated him with a Bruton's tyrosine kinase (BTK) inhibitor (ibrutinib) at a dose of 420 mg once daily (q.d.) for his CLL. For about two years, he received a quite successful treatment with methotrexate and the subcutaneously administered tumor necrosis factor (TNF) inhibitor (adalimumab) for his PsA, until his plaque psoriasis worsened. He consulted us when the severity of his skin condition necessitated a change in his treatment regimen. In the following discussion, we explore treatment options for this clinical scenario, with a particular focus on managing PsA in the context of CLL as a comorbidity. Additionally, we report on the initial phase of treatment with an anti-interleukin-23 (IL-23) inhibitor (guselkumab), specifically targeting his aggravated psoriasis.

Keywords

Introduction

The function of a healthy immune system involves CD4+ and CD8+ T cells which assist B cells to make antibodies and fight microbes together with natural killer cells and macrophages. The production of cytokines and chemokines is a critical element for this function. Depending on the cytokine milieu, previously uncommitted CD4+ T cells differentiate into Th1 or Th2 cells and, if activated, they produce distinct cytokine patterns [1]. Th1 cells can eradicate intracellular pathogens whereas Th2 cells rather fight extracellular pathogens. While the Th1 system plays a role in autoimmunity, aberrant Th2 responses are associated with allergy. A third subset of CD4+ T cells are Th17 cells which secrete interleukin-17 (IL-17).

These are pro-inflammatory and have a key role in the defense against extracellular bacteria and fungi but also in the development of autoimmunity. The secretion of IL-23 by antigen-presenting cells can activate Th17 cells [2, 3].

IL-23 and Th17 cells play an important role in immune-mediated diseases such as psoriasis [4, 5], PsA, and axial spondyloarthritis (axSpA). In chronic inflammatory bowel disease (IBD) drugs targeting the cytokine IL-23 work well but not agents blocking IL-17 [6, 7]. This is in contrast to axSpA, where only anti-IL-17 works, while both agents are efficacious in psoriasis and PsA [8–10]. In rheumatology, these agents are grouped under biologic disease modifying anti-rheumatic drugs (bDMARDs) while the Janus kinase inhibitors (JAKi) are targeted synthetic (ts) DMARDs.

The anti-IL-17 agents approved for psoriasis and PsA are secukinumab, ixekizumab, and bimekizumab, while the approved drugs targeting IL-23 are ustekinumab, risankizumab, tildrakizumab and guselkumab. The first IL-23 inhibitor (IL-23i), ustekinumab, targets the p40 subunit shared by IL-23 and IL-12, the other IL-23i are directed against the p19 subunit of IL-23. Anti-IL-23 agents are known to be efficacious also for nails, scalp, and hands [11].

Among the many JAKi, four currently play a role in rheumatology: tofacitinib, upadacitinib, baricitinib, and filgotinib. There are four JAKs to be inhibited: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), and the JAKi have different selectivity [12].

However, there are more options for the treatment of PsA including tumor necrosis factor inhibitors (TNFi), abatacept, and apremilas. The reintroduction of TNFi after the development of paradoxical psoriasis known to occur in < 5% of cases [13] treated with TNFi was not found to be very successful in a larger case series [14]. Abatacept has no strong effects on the skin in PsA. Of note, in patients with a history of malignancy, apremilast seems to safely work in patients with PsA [15].

Case report

A 76-year-old male patient had longstanding PsA for 15 years. The proximal interphalangeal (PIP) and the distal interphalangeal (DIP) joints, the fingernails, and the skin (plaque psoriasis) were involved. The patient had been treated with methotrexate 15 mg s.c./week and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen 400–1,200 mg on demand for 10 years, and in the last 2 years also with adalimumab 40 mg every 2 weeks. In October 2023 he experienced worsening of the nail and skin lesions—a problem known to occur with TNFi [13], while the joints hadn't worsened much.

In March 2022 chronic lymphocytic leukemia (CLL) had been diagnosed. The disease was treated with Bruton's tyrosine kinase inhibitor (BTKi) ibrutinib, dosed 420 mg once daily (q.d.) [16]. The treatment with TNFi was not considered as a risk factor for malignancy [17].

Taken all considerations together (see details in the discussion), we decided to treat our PsA patient with the serious comorbidity of CLL with the novel anti-IL-23 antibody guselkumab [9, 12].

Since, after the first two doses given 4 weeks apart there was only limited success, the hematologist decided to change the CLL treatment to zanubrutinib, a second-generation BTKi with enhanced target selectivity and occupancy of the kinase binding site, and superior efficacy for CLL [18]—also because ibrutinib may cause or worsen arthralgias [19].

When we saw the patient 3 months after the start of this regimen—the dosage of zanubrutinib was only 2 × 80 mg/day (approved dose 160 mg twice daily), ongoing methotrexate s.c. he reported having only minor joint symptoms using 400 mg of ibuprofen 2–3 times a week, no more skin lesions, and largely improved finger and toenails.

Discussion

This case is of interest because we had to search the literature for arguments in favor or against the available DMARDs.

In this regard, the role of Th17 cells in cancer has not been really clarified to date. Depending on the form of cancer, their activities can be either pro- or anti-tumorigenic. As the most predominant form of leukemia in the developed world, the B-cell malignancy CLL accounts for about 11% of all hematologic neoplasms [20, 21]. Complex interactions in the microenvironment support the survival of malignant B cells [22, 23]. However, dysfunctions in the T-cell compartment contribute to disease progression [24]. A terminally differentiated phenotype develops which is characterized by a low proliferation capacity and impaired immune functions. This defect in the T-cell immune response in CLL is considered a major factor for the development of secondary malignancies and infections, which contribute to the increased morbidity and mortality in this disease [25]. The increase in IL-17 serum levels and/or Th17 cells in CLL compared to healthy individuals shows some correlation with prognostic markers and changes in the tumor microenvironment [26]. However, the exact mechanisms how this contributes to CLL progression are not clear. The effects of CLL-targeted therapies on Th17 cells and their potential in therapies are incompletely understood. Nevertheless, Th17 cells are elevated in CLL patients with better prognostic markers and this correlated with longer survival [27]. There are also non-Th17 IL-17A-expressing cells in CLL such as maturing granulocytes and mature mast cells which may have an influence on the microenvironmental milieu in leukemic spleens hereby promoting the recruitment and/or expansion of Th17 and other IL-17-expressing cells [28]. In that study with many untreated CLL patients in different stages, higher Th17 and IL-17A values were associated with less progression of the disease, and lower Th17 and IL-17A values were seen in patients with unfavorable prognostic factors [27]. In addition, IL-17 was shown to be also able to induce IL-6 production [29]. Furthermore, the ability of Th17 cells to neutralize tumors was shown to be greater than that of Th1 polarized cells which was attributed to Th17 cells acquiring a Th17/Th1 phenotype that secretes interferon-γ (IFN-γ) [21, 30]. However, there are also somewhat conflicting data showing that the situation is not entirely clear yet [31, 32]. Nevertheless, in conclusion, we found that anti-IL-17 therapy was not a preferable option for our patient.

The literature on IL-23 is, in comparison to IL-17, sparse. Nevertheless, CLL cells activated in vitro have been shown to produce IL-23 and the presence of IL-23 in lymphoid tissues of CLL patients suggests that an autocrine/paracrine loop may induce cell proliferation in CLL. In accordance, interference with the IL-23 receptor (IL-23R)/IL-23 axis using an anti-IL-23p19 antibody showed effects in xenografted mice—suggesting potential therapeutic strategies [33]. In conclusion, we found no relevant arguments against anti-IL-23 treatment in our patients.

Tyrosine kinases (TKs) are enzymes that can transfer a phosphate group from adenosine triphosphate (ATP) to the tyrosine residues of specific intracellular proteins; they work as an on/off switching of cellular functions. Phosphorylation of proteins by kinases is a centrally important mechanism for signal transduction and regulating cellular activity. Accordingly, there are more than 50 FDA-approved TK inhibitors (TKi) [34]. A total of 90 human genes contain 94 protein TK domains. Four of those genes contain both, an active kinase and a so called pseudokinase domain—domains without catalytic activity: JAK domains JAK1, JAK2, JAK3, and the tyrosine-protein kinase domain TYK2 [35]. These proteins are associated with type I and type II cytokine receptors. The regulation of JAK involves cytokines including ILs, IFNs, and hemopoietins which can activate JAK to regulate the JAK-STAT pathway [14, 35]. The JAK1-dependent pathways include IFN-α/pSTAT5, IL-6/pSTAT, and JAK2-dependent and JAK3-dependent pathways include IL-2, IL-15, IL-4 (JAK1/JAK3), IFN-γ (JAK1/JAK2), granulocyte colony stimulating factor, IL-12, IL-23 (JAK2/TYK2) and granulocyte-macrophage colony-stimulating factor (JAK2/JAK2) [36]. Of note, a small-molecule TYK2 inhibitor, deucravacitinib, has recently been approved for moderate-to-severe plaque psoriasis [37].

BTKi play a crucial role in B-cell development, differentiation, proliferation, and survival [38]. Ibrutinib, an irreversible BTKi, is an approved oral targeted therapy for CLL but patients may have adverse events and, therefore, may need to reduce the dose or even have to stop treatment [39]. Another JAKi, ruxolitinib, with selectivity for JAK1 and JAK2, approved for more than 10 years, is used for the treatment of myelofibrosis, polycythemia vera, and acute graft-versus-host disease but failed to control and even accelerated CLL in clinical trials. Indeed, ruxolitinib may even release activating signals for CLL cells. Furthermore, JAK inhibition provided no added value for disease control in CLL patients [40].

Finally, there has been some discussion on the role of JAKi regarding the risk of malignancy [41] and major cardiovascular events (MACE) [42]. However, the risk of developing cancer in patients treated with JAKi was only increased relative to TNFi—agents which rather seem to reduce the risk [41]. Of note, cancers were rare in all comparisons. Furthermore, the risk of MACE was mainly increased in patients who already had cardiovascular events [42]. Taken together, we decided that therapy with a JAKi was not a preferable option for our patient. In conclusion, the treatment of our patient with PsA and CLL with the IL-23 inhibitor guselkumab had relatively good short-term efficacy after 3 months. The influence of co-treatment with BTKi needs further study in PsA and likely also many other diseases. We hope that it may be helpful for colleagues in a similar clinical situation to know what we have determined and considered in this case.

Abbreviations

BTKi: Bruton's tyrosine kinase inhibitor

CLL: chronic lymphocytic leukemia

DMARDs: disease modifying anti-rheumatic drugs

IFN-γ: interferon-γ

IL-17: interleukin-17

JAK: Janus kinase

JAKi: Janus kinase inhibitors

PsA: psoriatic arthritis

TKs: tyrosine kinases

TNFi: tumor necrosis factor inhibitors

TYK2: tyrosine kinase 2

Declarations

Author contributions

JB: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. KK: Investigation, Writing—review & editing. DP: Supervision, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

Jürgen Braun, who is the Associate Editor of Exploration of Musculoskeletal Diseases, had no involvement in the decision-making or the review process of this manuscript. The other authors declare that they have no conflicts of interest.

Ethical approval

The Ethical Committee of the Ärztekammer Berlin declared on February 12th, 2024 that no ethical vote was necessary for this case report.

Consent to participate

Informed consent to participate in the study was obtained from the participants.

Consent to publication

The patient has been informed about this publication, and he gave written consent.

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