Eligibility for biological treatment in patients with Atopic Dermatitis and chronic Hepatitis B virus infection: A case description and literature review

Kwalifikacja do leczenia biologicznego pacjentów z atopowym zapaleniem skóry i przewlekłym zakażeniem wirusem zapalenia wątroby typu B: opis przypadku i przegląd literatury

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Streszczenie

Obecnie coraz więcej pacjentów wymagających systemowej immunosupresji (SI) wykazuje wielochorobowość. Terapie te stwarzają poważne ryzyko reaktywacji utajonych, przewlekłych zakażeń, zwłaszcza wirusowego zapalenia wątroby typu B i C (WZW B, C). Stosunkowo bezpieczną alternatywą dla SI są leki biologiczne. W leczeniu pacjentów z atopowym zapaleniem skóry (AZS), o nasileniu umiarkowanym do ciężkiego, i przeciwwskazaniami do SI, takimi jak zakażenie WZW B, stosuje się z powodzeniem Dupilumab (DUPI), przeciwciało monoklonalne przeciwko IL-4R. Opisujemy przypadek pacjenta w takiej właśnie sytuacji klinicznej, zwracając szczególną uwagę na spersonalizowaną kwalifikację do leczenie biologicznego w perspektywie wytycznych na szczeblu krajowym i międzynarodowym. Przeprowadzono przegląd aktualnych danych klinicznych i eksperymentalnych dostępnych na temat opisanego zagadnienia. Praktyczne aspekty tej pracy mają na celu pokazanie procesu diagnostycznego i terapeutycznego w celu lepszego zrozumienia obecnych wytycznych dla terapii biologicznych, zgodnych z medycyną opartą na faktach.

Słowa kluczowe: atopowe zapalenie skóry, dupilumab, wirus zapalenia wątroby typu B, leczenie biologiczne

Summary

Nowadays, number of patients with multimorbidities and requiring systemic immunosuppression (SI) is increasing. These therapies pose serious risk of reactivation of latent, chronic infections, especially Hepatitis B and C viral infections (HBV, HCV). A relatively safe therapeutic alternatives to SI are biologicals. In treatment of patients with moderate-to-severe Atopic Dermatitis (AD) and contraindications to SI, such as HBV infection, Dupilumab (DUPI), a monoclonal antibody against IL-4R, is used with therapeutic success. We present such case description with emphasis of personalized eligibility for biological drug program in perspective of national and international qualification guidelines. Review of current clinical and experimental data regarding this problem was conducted. Practical aspects of this study are intended to show the diagnostic and therapeutic process to better understand current guidelines of evidence-based biological therapies.

Key words: atopic dermatitis, dupilumab, hepatitis B virus, biological therapy

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Introduction

Atopic dermatitis (AD) is one of the most common, chronic, inflammatory skin diseases, affecting 3.67%-16.76% of patients in Polish population. AD is typically considered a childhood disease, although prevalence in adult population is becoming a rising concern [1]. The incidence rate of AD has been increasing steadily throughout the years and it's estimated to rise in the future. Most common symptoms associated with AD are eczema, itching and skin dryness. The treatment usually relies on reducing symptoms, controlling inflammation, and preventing recurrence of exacerbations by proper skin care. The effectiveness of therapy is most commonly assessed by two separate scales, objective and subjective, respectively: Eczema Area and Severity Index (EASI) and Dermatology Life Quality Index (DLQI). Nowadays, treatment options for moderate-to-severe AD have been broadened by novel biological therapeutic options.

Hepatitis B virus (HBV) infection, affecting over 400 million people worldwide, is a major cause of cirrhosis, hepatocellular carcinoma, and acute hepatitis. Reactivated HBV infection caused by immunosuppressive drugs, commonly used in the field of dermatology, is becoming a rising therapeutic issue due to its potentially devastating complications.

Dupilumab (DUPI) is a monoclonal antibody against subunit alfa of the receptor for IL-4, selectively inhibiting IL-4 and IL-13. DUPI was the first biologic therapy approved for the treatment of moderate-to-severe AD. Biologics such as DUPI are a highly efficacious and safe treatment option for patients with immune-mediated disease; however, because of their modulation of the immune system, biologics have been associated with severe infections, including reactivation of latent HBV infection. Due to the increased morbidity and mortality associated with active HBV, physicians may have concerns regarding prescribing biologics in patients with chronic HBV infection. Increased populational life expectancy and constant development of new biological treatment options for various allergic diseases and immunological deficiencies means that more and more patients undergoing such therapies are multi-morbid.

The aim of this paper is to present a case of an AD and comorbid HBV infection in a patient successfully treated with DUPI and to discuss clinical management in the context of eligibility to biological drug programs and the current state of knowledge in the international literature.

Case description

Patients history

The patient is a 36-year-old Caucasian male, suffering from AD from the first months of his life. Since childhood, the variable intensity of symptoms has been controlled with topical corticosteroids and oral antihistamines. So far, symptoms have been controlled mainly with topical treatments and oral antihistamines on demand.

Current Exacerbations

Recent ailments started with localized skin changes, mainly covering lower limbs, painful, odorous lesions and extensive lichenification (thickening of the skin with increased skin markings).

In May 2021, the patient was hospitalized in the dermatology department due to severe exacerbation of AD with bacterial superinfection. The value of EASI was 54.2 and DLQI value was 12. After hospitalization, extensive chronic eczematous lesions persisted.

In December 2022, there was an exacerbation of AD related to family issues, which resulted in another hospitalization from December 27, 2022, to January 4, 2023. During this hospitalization, the patient had experienced generalized skin dryness, erythematous-exfoliative and infiltrative lesions, and bacterial superinfection. (Fig. 1) Additionally, subcutaneous swelling of the lower limbs and forearms with intense pain was present at admission. Occlusive dressings were applied upon skin changes of the lower limbs. Pharmacological treatment during hospitalization included oral corticosteroids, antihistamines, and tramadol.

Figure 1. Skin lesions on patient's lower limbs during hospitalization in dermatology clinic in 2022.

During the post-hospitalization visit on January 30, 2023, the presence of erythema covering a large part of the trunk, arms, forearms, forehead and lower back has been ascertained. Lichenification could be seen on the skin of the back, wrists, and dorsal surfaces of the hands.

Qualification for biological treatment

On an outpatient visit after hospitalization, the patient unexpectedly reported HBV infection of unknown origin, not previously assessed by a medical doctor. Laboratory assessments showed a total IgE of 3313 kU/L and CRP levels of 5.7 mg/L. Proper medical documentation on HBV serological tests was absent. Further diagnostics confirmed suspected HBV infection. (Tab. 1.) Due to the moderate risk of HBV reactivation, immunosuppressive treatment with cyclosporine was not initiated, which is indicated in patients on a standard treatment regimen. Treatment was consulted with an infectious disease specialist. There were no contraindications to biological treatment. Serological surveillance for moderate risk of HBV reactivation was advised. At the initiation of therapy, the EASI value was 44.6 and DLQI value was 12.

Table 1. Relevant baseline serological and laboratory tests values upon patient's qualification to the AD treatment program.

LABORATORY INVESTIGATIONS	**RESULTS**	**REFERENCE VALUES**
Creatinine	69.7 µmol/L	49.0 – 90.0 µmol/L
GFR	116.1 mL/min/1.73m^2	> 90 mL/min/1.73m^2
Urea	5.84 mmol/L	2.8 – 7.2 mmol/L
ALT	28.4 U/L	0 – 35 U/L
AST	27.1 U/L	0 – 35 U/L
Total bilirubin	11.7 µmol/L	5.0 – 21.0 µmol/L
Total protein	69.4 g/L	66.0 – 83.0 g/L
HBs antigen	Present (+)	
DNA-HBV	Absent (-)	
Anti-HBs antibodies	Not reactive (-)	

Treatment outcomes

Dupilumab treatment was started on April 21, 2023. At first evaluation during treatment on August 23, 2023 the EASI dropped down to 0,02 and DLQI to 3 points. Considerable decrease in EASI and DLQI values has been consistently observed at next follow-up visits. Upon recent evaluation in June 2024 the EASI value was 7.2 and DLQI value was 2 points. During biological therapy, liver function tests and DNA-HBV were regularly monitored and no HBV infection reactivation has been ascertained.

Discussion

Dupilumab is the first biologic therapy approved for the treatment of moderate-to-severe AD. HBV reactivation in patients with chronic infection is a serious complication associated with many biologics, mainly those agents targeting B cells and TNF-alpha. Systemic treatment with cyclosporine, tacrolimus, or selected immunological pathways inhibitors (namely TNF-alpha inhibitors i.e. infliximab, adalimumab; B cell activation inhibitors i.e. rituximab and ofatumumab; anthracyclines i.e. doxorubicin [6]) in patients with AD and concomitant HBV infection is not recommended [2]. There is limited data regarding safety of biologics for AD in patients with HBV infection [3].

Eligibility for drug programs in multi-morbid patients

First-line treatment of moderate-to-severe AD involves systemic immunosuppressants, such as cyclosporine, a calcineurin inhibitor. [4] HBV-positive patients treated with cyclosporine are at higher risk of HBV reactivation [2]. DUP clinical trials excluded HBV-positive patients, therefore DUP safety in HBV infection was not fully evaluated until recent reports of successful biological treatments in described patients' population [5].

Dupilumab is financed in Poland within the frame of the treatment program for patients suffering from severe AD aged 6 and above [6]. The drug program includes, patients for with EASI value 20 and more, in whom treatment with cyclosporine is ineffective, results in side effects or is contraindicated. This last situation was present in the described patient. Apart from dupilumab, other treatments currently available in Poland within the same severe AD treatment program include tralokinumab – a monoclonal antibody against IL-13 as well as Janus kinase inhibitors (JAKi): upadacitinib, baricitinib and abrocitinib.

Marketing authorization for dupilumab in the European Union states that it is designed for the treatment of moderate-to-severe atopic eczema in patients who are candidates for systemic therapy [7]. The requirement for prior attempt of AD treatment with systemic immunosuppressive agent before considering dupilumab is present in the reimbursement regulations in many countries. The UK National Institute for Health and Care Excellence (NICE) recommends dupilumab in adults not responding to at least one earlier systemic therapy or in whom such therapy is contraindicated or not tolerated [8]. Failure of cyclosporin treatment, its intolerance or presence of contraindications to immunosuppression has also been mentioned in recommendations for adult dupilumab treatment of AD issued, among others, in France [9], Italy [10] Ireland [11] as well as in other countries, although specific requirements regarding type of systemic immunosuppression may vary. JAK inhibitors incur more than 10-percent risk of reactivation of latent infection, including hepatitis B. Therefore, proper infection testing is required before their administration, including HBs antigen presence, anti-HCV antibodies, interferon-gamma release assays (IGRAs) for latent tuberculosis or tuberculin test as well as HIV Ag/Ab combo tests.

In case of DUPI, as a moderate risk biologic agent with regard to reactivation of HBV infection, the above mentioned testing is not required before qualification to the program [6].

Expert consensus on a systemic treatment of AD with HBV coinfection from 2023 suggests that:

1. Patients with HBV infection who are surface antigen positive should be evaluated for concomitant therapy for HBV prior to starting any oral systemic treatment for AD (83 % agreement), and

2. If there are barriers to accessing concomitant therapy for HBV, biologic therapies with proven efficacy in AD are the preferred option (92 % agreement) [12].

According to Recommendations of the Working Group for prevention of HBV reactivation from 2019 for the HBsAg-positive and anti-HBc-negative patients

scheduled for therapy with drugs associated with a high risk of reactivation should begin the prophylaxis of HBV reactivation with nucleotide analogues (NAs) with high potency (the group comprises entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) [13].

Clinical data on AD treatment with DUPI in HBV-positive patients

There have already been clinical reports describing positive treatment results and lack of virological reactivation in patients with AD and chronic HBV infection treated with DUPI. Earlier studies, conducted before the national treatment programs were widely available, did not clarify whether DUPI could favor HBV reactivation.

In 2021, Matsutani M et al. investigated safety of DUPI in HBV-positive patients. Of the 112 AD patients who started DUPI therapy, 6 patients were initially suspected of HBV coinfection and 5 patients (4.46%) were HBsAb positive and did not receive vaccination in the past. Throughout 100 weeks of biological therapy only one patient became HBV-DNA positive (without any clinical abnormalities), and HBV-DNA came back negative in next follow-up until the end of the study. Authors concluded that DUPI can be administered to HBV-positive AD patients with careful monitoring [5].

In 2019, Ly K et al. presented 2 cases of patients with AD and concomitant HBV infection, controlled before biological therapy using systemic immunosuppression with cyclosporine and anti-viral prophylaxis with entecavir, obtaining unsatisfactory results. Treatment with DUPI was done with close surveillance of liver function and HBV status before and during treatment. Concurrent topical treatment and Goeckerman therapy (UVB phototherapy and coal tar) were also applied. The patients achieved significant improvement of AD symptoms with no clinical evidence of hepatitis or HBV reactivation and an undetectable viral presence [15].

Experimental research on Th1 and Th2 response pathways in the context of AD treatment with DUPI

Imay Y et al. have showed experimentally potential explanation for the safety of DUPI treatment in concomitant HBV infection is present. DUPI is a monoclonal antibody against subunit alfa of receptor for IL-4, selectively inhibiting IL-4 and IL-13 related pathways. This mechanism of action leads to suppression of Th2 immune responses, effectively treating AD. HBV suppression occurs through an immunological mechanism of Th1 response, therefore DUPI therapy is unlikely to cause HBV reactivation [16]. Clinical characteristics and results of patients with AD and chronic hepatitis B virus infection treated with DUPI, as shown by Matsutani M et al., seems to confirm hypothesis of selective Th1 response pathway inhibition [5].

Studies have marked possible interactions between IL-4, a pleiotropic anti-inflammatory cytokine involved in hepatic immune system modulation, and HBV infection [17]. Specific IL-4 subtypes have been associated with more severe progression of chronic HBV development. Moreover, certain IL4 gene polymorphisms have been recognized as a protective hepatic factors and have been associated with slower progression to cirrhosis in patients with HBV infection. For example, IL-4-590C/T genotype was found to play a vital protective function in development of hepatitis among HBV infection carriers [18].

Conclusions

This case illustrates the challenges of treating atopic dermatitis in patients co-infected with HBV. Collaboration between immunologists, dermatologists, and infectious disease specialists ensures implementation of safe and effective treatment strategies. Systemic immunosuppression in patients with AD and co-infection with HBV is discouraged, therefore biological treatment may be a safer therapeutic option. Knowledge of national drug programs is crucial for treating patients in less common and multi-factorial clinical situations with the best possible therapies and according to current, evidence-based standards.

To our knowledge, there is no comprehensive meta-analysis regarding DUPI administration in patients with AD and HBV co-infection. Although further research needs to be done, real-life data suggests highly beneficial results of biological therapy and moderate risk of HBV reactivation. Eligibility for biological drug programs constitutes a major step in diagnostic and treatment process of multi-morbid patients care and needs to be carefully evaluated individually for every patient. In the context of this case report, we are highlighting potential difficulties what may be encountered by dermatologists and allergists when confronted with the need for therapy with biologics or JAK inhibitors in patients with severe AD and chronic infectious comorbidities, as exemplified by hepatitis B. These difficulties are sequel to specific regulations contained in many national reimbursement schemes for biologics and/or JAKi in AD treatment and associated with requirement of proving inefficacy, intolerability or contraindications to systemic immunosuppressive treatment.

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