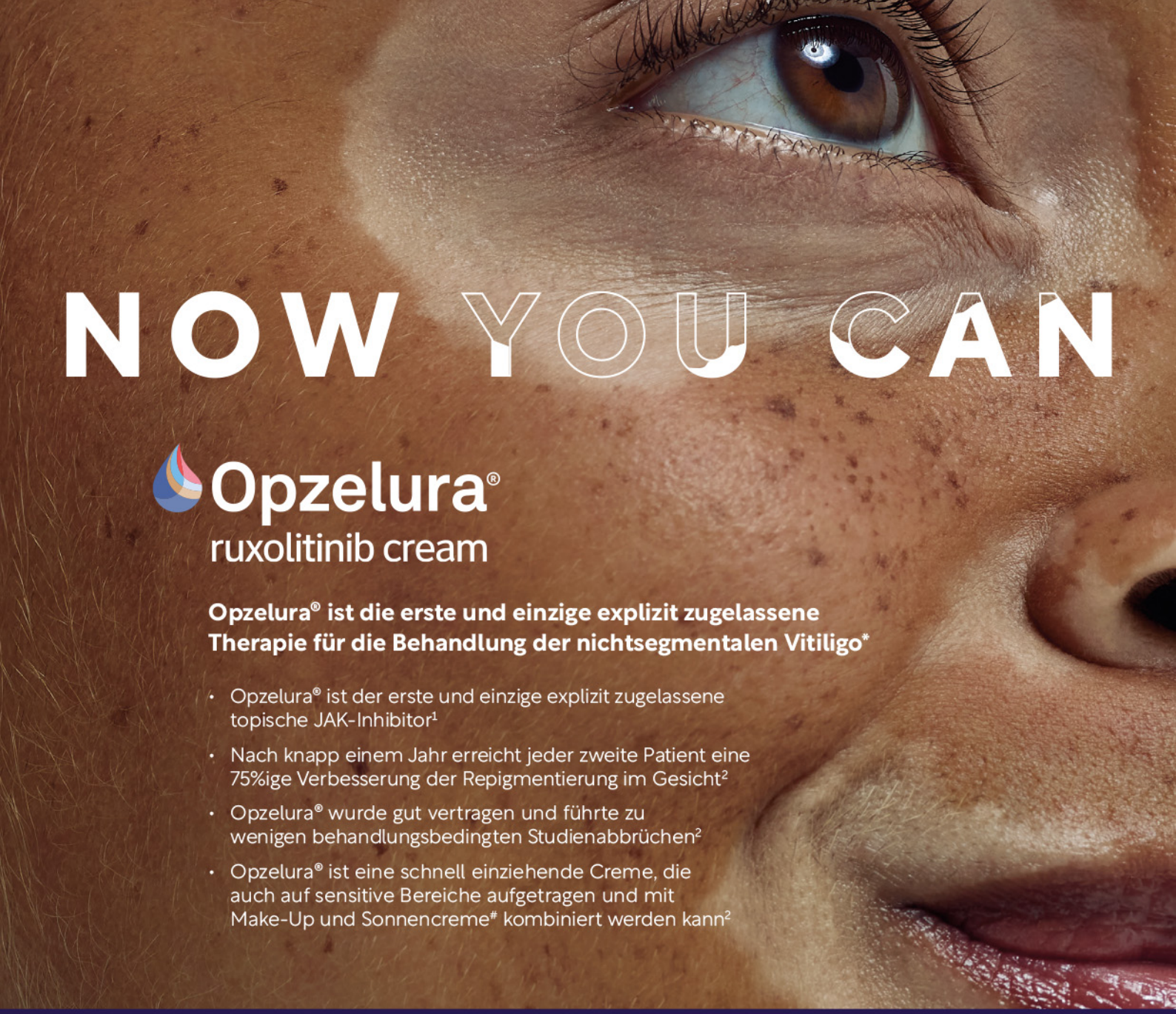

Opzelura®
ruxolitinib cream

Opzelura® ist die erste und einzige explizit zugelassene Therapie für die Behandlung der nichtsegmentalen Vitiligo*

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MEHR ERFAHREN

Incyte Dermatology

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# Sonnencreme sollte frühestens 2 Stunden nach der Anwendung von Opzelura® aufgetragen werden.[1]

Referenzen:

1. Aktuelle Fachinformation Opzelura®.
2. Rosmarin D, Passeron T, Pandya AG, et al. Two Phase 3, randomized, controlled trials of ruxolitinib cream for vitiligo. N Engl J Med. 2022;387(16):1445-1455.

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MINIREVIEW

Wheat-dependent exercise-induced anaphylaxis: subtypes, diagnosis, and management

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Summary

Wheat-dependent exercise-induced anaphylaxis (WDEIA) is an IgE-mediated food allergy with allergic symptoms ranging from intermittent urticaria to severe anaphylaxis that occurs when wheat ingestion is combined with augmenting cofactors such as exercise, non-steroidal anti-inflammatory drugs, or alcohol. In most cases, patients are identified by sensitization to ω5-gliadins in the gluten fraction of wheat. ω5-gliadin-negative subtypes of WDEIA are often difficult to diagnose and may be caused by Tri a 14 (wheat lipid transfer protein), after percutaneous sensitization with hydrolyzed wheat proteins, or, in rare cases, by cross-reactivity to grass pollen. Diagnosis is established based on the patients' history in combination with serum IgE profile, skin testing, basophil activation tests, and challenge tests with cofactors. Individual dietary counselling remains the central pillar in the management of WDEIA patients. A completely wheat-free diet is a possible option. However, this appears to promote tolerance less than continued regular consumption of gluten-containing cereals in the absence of cofactors. All patients should have an emergency set for self-treatment including an adrenaline autoinjector and receive adequate instruction. More data are needed on sublingual immunotherapy for WDEIA, a potentially promising therapeutic prospect. This article provides an overview of current knowledge on the diagnosis and management of WDEIA including an optimized challenge protocol using wheat gluten and cofactors.

INTRODUCTION

In wheat-dependent exercise-induced anaphylaxis (WDEIA), IgE-mediated allergic symptoms occur when wheat ingestion is combined with augmenting cofactors, such as exercise, non-steroidal anti-inflammatory drugs (NSAID) or alcohol.[1] Wheat is not only the most predominant allergen for food-dependent exercise-induced anaphylaxis (FDEIA), it is also the most common food elicitor of anaphylaxis in adults in Central Europe, accounting for approximately 15% of food anaphylaxis cases.[2] While a non-cofactor-associated wheat allergy is most common amongst children, WDEIA is more prevalent among teenagers and adults.[3]

Males and females are equally affected, and compared to other food allergies, fewer patients seem to suffer from atopic comorbidities.[2] In many cases, WDEIA is the patient's only (food) allergy.[3]

The severity of symptoms ranges from intermittent urticaria or angioedema – which is why WDEIA should always be kept in mind in such cases – to severe anaphylaxis, with reactions often being more severe than in other food allergies.[2,4] These symptoms are elicited – mostly with a quick onset – when wheat is ingested less than 4 hours

before or after occurrence or consumption of cofactors, but even longer time intervals have been described.[1,5] As the name suggests, exercise is the most frequent cofactor leading to reactions, as are NSAID and alcohol in decreasing order of frequency.[6] However, many other – partly highly individual – cofactors exist, such as stress, infections, the menstrual cycle, temperature changes or temperature extremes[3] and the combination of different cofactors seems to further decrease the reaction threshold.[7] This may be a key factor for the observation that despite regular wheat intake, even in presence of cofactors, allergic reactions occur only infrequently in many patients.[3,4]

The pathophysiological mechanisms underlying WDEIA have not yet been elucidated: different hypotheses have been proposed, including that the cofactors may lead to an increased gastrointestinal permeability and thus to higher plasma gliadin levels, finally leading to a reaction in WDEIA patients.[8,9] In a recent publication by Morita and colleagues, it was shown that cofactors might increase gastrointestinal gliadin absorption by inhibition of prostaglandin production.[10] However, the evidence is still incomplete, and the literature is contradictory about whether cofactors can lead to enhanced plasma gliadin levels in healthy individuals.[1,10–12] Other proposed mechanisms include an increased tissue glutaminase activity in the gut due to the cofactors or a potential effect of exercise-induced blood flow redistribution.[1]

Unfortunately, the diagnosis of WDEIA is still often delayed for many years,[3,6,13] resulting in not only a physical, but also a severe psychological burden for many patients.[14]

ALLERGENS AND DIFFERENT SUBTYPES OF WDEIA

The major allergen in WDEIA are the ω5-gliadins in the gluten fraction of wheat, with ω5-gliadin specific IgE (sIgE) test (ImmunoCAP® assay, Phadia, Uppsala, Sweden) showing a high sensitivity (up to 80%) and specificity (approximately 96%).[12,13,15,16] Therefore, "ω5-gliadin allergy" is sometimes used as synonym for WDEIA.[6] However, there are also other allergens relevant in this disease.

Besides ω5-gliadins, high-molecular-weight glutenin subunits (HMW-GS) are another important allergen in WDEIA.[12,17] Other potential allergens from the wheat gluten fraction include low-molecular-weight glutenin subunits (LMW-GS) and α/β/γ-gliadins.[15,17,18]

Among the non-gluten allergens, some cases of ω5-gliadin-negative WDEIA may be caused by wheat lipid transfer protein Tri a 14. Unlike for ω5-gliadins, an asymptomatic sensitization to Tri a 14 is frequent, rendering oral challenge tests even more indispensable to diagnose Tri a 14-WDEIA.[19] Other features of Tri a 14-WDEIA include a stronger association with atopy and higher cross-reactivity with other foods such as nuts or other cereals.[19]

Another subtype of ω5-gliadin-negative WDEIA is caused by percutaneous sensitization to hydrolyzed wheat proteins (HWP), frequently used in soaps, shampoos, and other cosmetics. In Japan, over 1300 patients developed HWP-WDEIA after using a HWP-containing soap. Many of these patients first developed local symptoms when using the product, and later all of them developed WDEIA symptoms: most commonly eyelid oedema, but also anaphylaxis was observed after ingestion of natural wheat products combined with cofactors.[20] In Europe as well, cases of HWP-WDEIA caused by cosmetics have been reported.[21]

More recently, another new subtype of ω5-gliadin-negative WDEIA has been proposed, related to grass pollen allergy.[22] While asymptomatic cross-sensitization to wheat is quite common (approximately in 65%) in grass pollen allergic subjects, Ogino and colleagues reported that in individual patients, strong grass pollen sensitization could be the cause for ω5-gliadin-negative WDEIA (not caused by HWP or Tri a 14), possibly due to cross-reactivity of peroxidase-1 and beta-glucosidase between grass pollen and wheat.[22]

Taken together, especially the diagnosis of ω5-gliadin-negative WDEIA remains challenging, and patients suspected of having this allergy should therefore be referred to specialized centers. We are actively recruiting patients to study the mechanisms leading to WDEIA.

DIAGNOSIS OF WDEIA

The first step in diagnosing WDEIA is the acquisition of an accurate medical history. As described above, the fact that a patient describes regular tolerance of wheat should not invalidate the suspicion of WDEIA. Special emphasis should be placed in actively asking about the presence of potential cofactors in association with reactions, such as physical activity, NSAID, stress, alcohol, temperature extremes, or infections. Most importantly, WDEIA should always be considered as differential diagnosis for patients presenting with a presumable idiopathic anaphylaxis, NSAID intolerance, or intermittent urticaria.[4]

A skin prick test should be performed not only with whole-wheat extract or native wheat flour, but also with wheat gluten, as this has shown the best diagnostic value.[23] For the diagnosis of HWP-WDEIA, products containing HWP (if possible, products used by the patient) or pure HWPs should be tested.[20] For the diagnosis of WDEIA and to study different potential allergens, we are currently using the skin prick test panel shown in Table 1.

In patients with WDEIA, sIgE to whole-wheat extract may be negative, so sIgE to ω5-gliadins should always be determined directly.[12] Additionally, sIgE to Tri a 14 and gliadins should also be determined.[15,19] In many cases, these values will be negative in HWP-WDEIA, a fact that should not discourage from performing an oral challenge test, if the history is compelling. If grass-pollen-related WDEIA is suspected, sIgE to grass pollen should be assessed. In all cases with anaphylaxis, basal serum tryptase levels should be determined.

TABLE 1 Skin prick test panel for the diagnosis of WDEIA and the assessment of different potential allergens as used at the Technical University of Munich.

Test substance	Wheal	Erythema
Native wheat flour		
Wheat gluten		
Gliadins		
HMW-GS		
LMW-GS		
Native spelt flour		
Spelt gluten		
Rye flour		
Amylase trypsin inhibitors		
HWP 1		
HWP 2		
HWP 3		
HWP 4		
HWP 5		
Positive control		
Negative control		

Amylase trypsin inhibitors: 5 mg/ml; remaining substances used unconcentrated prick-to-prick. *Source of reagents:* wheat flour, wheat gluten, spelt flour, rye flour and Amylase trypsin inhibitors (Merck, Darmstadt, Germany) – commercially available; gliadins, HMW-GS, LMW-GS – produced and supplied by Leibnitz-Institute for Food Systems Biology at the Technical University of Munich, Freising, Germany); HWP 1–5 – supplied by manufacturers.
Abbr.: HMW-GS, high-molecular-weight glutenin subunits; LMW-GS, low-molecular-weight glutenin subunits; HWP, hydrolyzed wheat proteins.

The basophil activation test (BAT) has not yet been included in the standard diagnostic procedure in WDEIA. However, BAT can differentiate between WDEIA patients and controls, showing the individual sensitization patterns to different wheat allergens of patients with WDEIA.[17] The test has also shown potential in diagnosing HWP-WDEIA.[20]

Even though the oral challenge test remains the gold standard for diagnosing food allergies, the need for adding cofactors and lack of a standardized and widely accepted challenge protocol had hampered its utility in WDEIA. Challenges with normal wheat products and cofactors are problematic due to a high number of false-negative outcomes[3], which can be overcome by using pure wheat gluten with cofactors.[23] With 10 g of gluten being equivalent to approximately 125 g of wheat flour,[23] far higher allergen doses can be achieved, compensating for the potential lack of individual cofactors during the challenge test.

CHALLENGE PROTOCOL WITH WHEAT GLUTEN AND COFACTORS

Over many years, we have optimized gluten challenge testing for the diagnosis of WDEIA[23] and recommend the protocol shown in Figure 1, which delivers excellent results at the Technical University of Munich. Gluten buns can be prepared by mixing wheat gluten with double the amount of water, shaking the mixture well in a jar until a bun forms and baking it for 20 minutes at 200 °C.[23] In our experience, many patients (around 40%) will show mild reactions already on day 2, even without exercise and with only acetylsalicylic acid (ASA) as cofactor – this makes this protocol well feasible in everyday life, as exercise testing is often time-consuming and staff intensive.

In patients who have not recently taken or tolerated ASA, a separate ASA challenge may be needed if a reaction occurs on day 2. This may be performed either before the gluten challenge begins or on a separate appointment thereafter.

Patients with a high reaction threshold – which is not uncommon especially in ω5-gliadin-negative WDEIA patients – may need even higher doses of gluten and cofactors.[23] In contrast, reactions may occur already on

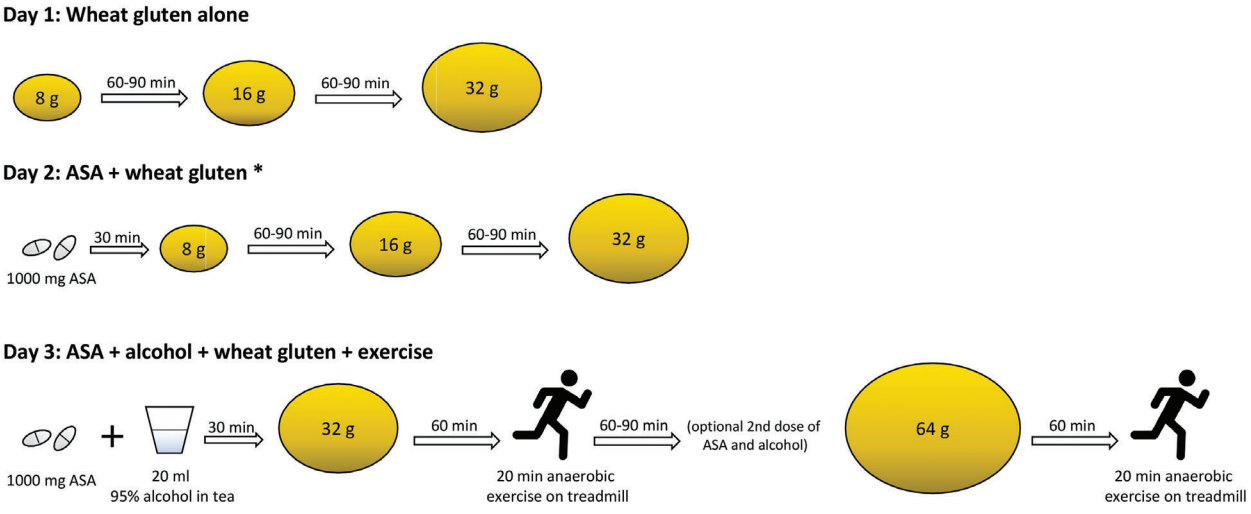

FIGURE 1 Proposed challenge protocol for the diagnosis of WDEIA. *If patients do not report to regularly tolerate ASA, a separate ASA challenge may be needed. *Abbr.:* ASA, acetylsalicylic acid; min, minutes; ml, milliliters

day 1 if the threshold is low.[7,13] As soon as an objective reaction confirming the diagnosis is evident, antiallergic treatment should be performed and blood tryptase levels should be assessed.[24]

MANAGEMENT OF WDEIA

As acute treatment in the event of a reaction, physical exertion and wheat consumption should be discontinued immediately and antiallergic medication should be applied depending on symptomatology.[24] An emergency set for self-treatment including an adrenaline autoinjector should be prescribed together with adequate instruction.

After diagnosis, patients should receive individualized dietary counselling to discuss the management of their disease. Among other aspects, the patients' individual reaction threshold based on history and challenge test should be considered. Although rye and barley do not contain ω5-gliadins, a potential cross-reactivity has been described and the clinical tolerance of these cereals in WDEIA remains unclear.[25,26]

A diet totally free of wheat and cross-reactive cereals may be chosen especially for patients with a low reaction threshold or based upon the patient's personal preferences, whether for convenience or for psychological reasons.[14] In most other cases, situational avoidance should be discussed, allowing patients to eat adjusted quantities of gluten-containing cereals if consumption is separated from cofactors such as exercise by at least 4–6 hours. It has been shown that this second approach can lead to an increase in tolerance, in contrast to a decrease in reaction threshold for patients following a strict dietary adherence.[27]

Sublingual immunotherapy with wheat gluten could represent a novel therapeutic approach for WDEIA patients in the future. A marked increase in reaction threshold levels could be achieved in a small pilot study with three patients, with sublingual immunotherapy over three years,[28] but studies on a larger patient collective are needed.

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CONFLICT OF INTEREST

None.

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