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The IL-36 Connection: Immunology's Role in GPP Pathogenesis and Therapy

Announcer:
Welcome to CME on ReachMD. This activity titled *The Interleukin 36 Connection: Immunology's Role in GPP Pathogenesis and Therapy* is jointly provided by the France Foundation and the American Association of Immunologists. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Fernandez:
Welcome to our continuing education activity titled *The Interleukin 36 Connection: Immunology's Role in GPP Pathogenesis and Therapy*. This continuing education activity is provided by the American Association of Immunologists and the France Foundation. The steering committee for this activity included myself, Dr. Anthony Fernandez, and my colleague, Dr. Johann Gudjonsson. I will be serving as your guide today as you navigate through this activity.

This activity features three cases: Case 1, understanding interleukin 36 signaling and GPP; Case 2, differentiating GPP from other dermatoses; and Case 3, GPP management plan using targeted therapy.

Welcome to this case-based activity on generalized pustular psoriasis. Over the next 10 to 12 minutes, you'll analyze a patient case to understand the critical role of interleukin 36 signaling in GPP pathogenesis.

Let's meet our patient, a 42-year-old woman who presents with a sudden diffuse skin eruption accompanied by high fever and systemic symptoms. She also has severe fatigue, malaise, and a painful burning sensation on her skin. She has no personal or family history of psoriasis. The rapid onset over just 3 days, combined with significant systemic symptoms, should raise concern for a serious inflammatory condition that involves the skin.

As we work through this case, consider what key features might help you narrow your differential diagnosis and understand the underlying pathophysiology.

Pause here and consider: what's your next move? This patient has an acute cutaneous eruption with systemic symptoms. Based on the patient's presentation, what would be your most important next step?

The answer is B, perform a detailed skin examination to characterize the eruption. While it might be tempting to treat empirically or order labs first, a thorough skin examination is essential to characterize the morphology and distribution of the skin lesions. This clinical information will help guide all subsequent diagnostic and therapeutic decisions.

Your thorough skin examination reveals striking findings: widespread erythema studded with multiple sterile pustules covering more than 1/2 of her body surface area. The patient also appears systemically ill with fevers and tachycardia. This constellation of findings, acute onset, widespread pustular rash, and significant systemic symptoms, should prompt consideration for generalized pustular psoriasis.

Consider what diagnostic information would be most valuable. Which tests would help confirm your suspected diagnosis and assess disease severity? All of these tests provide valuable information in GPP. The CBC will likely show neutrophilia. Inflammatory markers will be elevated, reflecting systemic inflammation. And a biopsy is strongly recommended to confirm GPP and to rule out other conditions. Metabolic abnormalities like hypocalcemia and hypoalbuminemia are also common. Genetic testing, while not required for

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diagnosis, can identify mutations that explain the disease pathogenesis, following confirmation of a GPP diagnosis.

The laboratory results confirm significant systemic inflammation and are consistent with generalized pustular psoriasis. Note the marked neutrophilia, over 18,000 white blood cells with 82% neutrophils, along with dramatically elevated inflammatory markers. The hypocalcemia and hypoalbuminemia reflect the metabolic complications that can accompany severe GPP. Most importantly, the skin biopsy shows the characteristic histopathologic features: neutrophilic subcorneal pustules and the pathognomonic spongiform pustules of Kogoj. The sterile cultures rule out infection. These findings collectively strongly support a diagnosis of GPP.

Genetic testing reveals a critical finding. Our patient has a homozygous mutation in the IL36RN gene. This gene encodes the interleukin 36 receptor antagonist, or IL-36Ra, a protein that normally acts to inhibit interleukin 36 signaling. Mutations in IL36RN are found in about 1/4 to 1/3 of GPP patients, and explain the disease pathogenesis. A homozygous mutation means both copies of this gene are affected, resulting in complete loss of IL-36Ra function. This genetic finding not only confirms the diagnosis but also has important implications for understanding the disease mechanism, and potentially for family planning counseling. Patients with identified mutations should be offered genetic counseling, especially women of childbearing potential, as mutations may affect pregnancy outcomes and postpartum flare risk.

To understand this patient's disease, we need to understand normal interleukin 36 signaling. Interleukin 36 is part of the interleukin 1 superfamily, and plays an important role in innate immunity at barrier surfaces like the skin. In healthy individuals, keratinocytes produce small amounts of interleukin 36 cytokines, alpha, beta, and gamma. These cytokines bind to the interleukin 36 receptor on keratinocytes and other cells, triggering activation of signaling cascades within cells that lead to inflammation and immune responses.

However, this signaling is tightly controlled by the interleukin 36 receptor antagonist, or IL-36Ra, which acts as an inhibitor of interleukin 36 signaling. IL-36Ra competes with interleukin 36 cytokines for binding of the same receptor, but doesn't activate it, effectively blocking excessive signaling. Think of it as a balance: normal IL-36 activity for appropriate immune responses, with IL-36Ra preventing immune system overactivation. This equilibrium is critical for healthy skin function.

Now let's see what happens in our patient with the IL36RN mutation. Without functional interleukin 36 receptor antagonist, there's no brake on IL-36 signaling. The pathway becomes unopposed and dysregulated. Excess interleukin 36 binds to receptors on keratinocytes, triggering intense activation. These activated keratinocytes become chemokine factories, producing massive amounts of CXCL1, CXCL2, and CXCL8, all potent neutrophil attractants. This creates a chemokine gradient that attracts neutrophils from the bloodstream into the skin.

But here's where it gets particularly problematic. Those recruited neutrophils release proteases that activate even more interleukin 36 precursors, which further activate keratinocytes, which produce more chemokines, which recruit more neutrophils. This vicious cycle, this amplification loop, drives the characteristic pustular inflammation of GPP. The neutrophils accumulate in the epidermis, forming the subcorneal pustules that we saw on our patient's biopsy. This is the fundamental mechanism of generalized pustular psoriasis pathogenesis: unopposed interleukin 36 signaling leading to excessive neutrophil recruitment and inflammation.

Now that you understand the interleukin 36 pathway in GPP, consider which features of this case reflect IL-36-driven pathogenesis. Select all features that are consistent with IL-36 dysregulation. Think about what unopposed interleukin 36 signaling would cause clinically.

All of these features are characteristic of IL-36-driven generalized pustular psoriasis. The rapid onset reflects the explosive nature of unopposed interleukin 36 signaling. GPP associated with IL36RN mutations typically occurs without prior plaque psoriasis. The widespread pustulation, systemic inflammation with fever and neutrophilia, all result from the interleukin 36 chemokine neutrophil axis we just reviewed, and the genetic mutation explains why this pathway is dysregulated in our patient.

Our patient's case demonstrates how a genetic defect in interleukin 36 regulation manifests as generalized pustular psoriasis. Her homozygous IL36RN mutation eliminates the normal regulatory inhibition on interleukin 36 signaling, leading to the explosive pustular eruption and systemic inflammation we observed. Important clinical considerations include the need for ongoing monitoring, as GPP is characterized by unpredictable flares. Given the genetic nature of her disease, genetic counseling is recommended, particularly regarding inheritance patterns and pregnancy planning, as IL36RN mutations may affect pregnancy outcomes and increase postpartum GPP flare risk. Remember, GPP is a systemic inflammatory condition requiring comprehensive management beyond the skin.

Let's summarize the key teaching points. First, IL-36 pathway dysregulation is central to GPP pathogenesis. When IL-36 receptor antagonist is deficient due to mutations, IL-36 signaling becomes unopposed, driving disease activity. Second, recognize the characteristic features: rapid onset, widespread pustulation without underlying plaques, and significant systemic inflammation. Third, understand the genetic predisposition: nearly 1/4 to 1/3 of GPP cases involve IL36RN mutations, though other genes are also

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implicated. Finally, remember the mechanistic axis: unopposed interleukin 36 activates keratinocytes which produce chemokines that recruit neutrophils which release proteases activating interleukin 36 precursors, creating an amplification loop. This interleukin 36 chemokine neutrophil axis is the engine of GPP pathogenesis.

Let's summarize what we have discussed about how interleukin 36 pathway dysregulation drives generalized pustular psoriasis. The key concept is that loss of interleukin 36 receptor antagonist function leads to unopposed signaling, excessive neutrophil recruitment, and the characteristic pustular inflammation of GPP.

One, prioritize early recognition of interleukin 36-driven features. Look for rapid onset within hours or days of widespread pustules on previously unaffected skin and significant systemic symptoms. These are the hallmarks of unopposed interleukin 36 signaling.

Two, use targeted diagnostic tests when GPP is suspected. Order a CBC, inflammatory markers, and skin biopsy early to confirm neutrophil-driven pathogenesis.

Three, treat GPP as a systemic inflammatory emergency. Unopposed interleukin 36 signaling can escalate quickly. Prompt evaluation and early systemic treatment, especially when fever, tachycardia, and metabolic abnormalities are present, can prevent complications.

Four, incorporate the interleukin 36 pathway into patient and team education. Explain how dysregulated interleukin 36 signaling drives the clinical picture. Understanding this mechanism supports clear communication about disease severity, genetic risk, and rationale for targeted therapies.

Five, consider interleukin 36RN genetic testing in patients with severe, atypical, or early onset pustular presentations, even without plaque psoriasis, to identify IL-36Ra deficiency and guide counseling on disease course and family planning.

Let's continue to Case 2, focusing on differentiating generalized pustular psoriasis from other dermatoses. Over the next 10 to 12 minutes, you'll work through a challenging diagnostic case to develop your skills in using clinical tools, biomarkers, and immunological markers to make accurate diagnoses.

Let's meet our patient, a 35-year-old man who presents to the emergency department with an acute, widespread pustular eruption accompanied by high fever and severe systemic symptoms over 3 days. Here's the important history: he took a course of amoxicillin-clavulanate 3 weeks ago for sinusitis, completing the full 10-day course. His symptoms began 11 days after finishing the antibiotic, not during active treatment. He has no personal history of psoriasis, but his mother has well-controlled plaque psoriasis.

This presentation raises important diagnostic questions. Could this be drug-induced AGEP despite the delayed timing? Or is this generalized pustular psoriasis triggered by medication or occurring de novo? The temporal relationship is atypical for AGEP, and the family history adds complexity. As we work through this case, you'll learn how to systematically differentiate these conditions.

Pause and think: When you're faced with acute pustular eruptions with recent drug exposure, what information matters most? Consider what would help you differentiate between GPP and drug-induced AGEP. Given the temporal relationship between antibiotic use and symptom onset, what information would be helpful in your initial assessment?

The correct answer is all of these choices. All of these elements are crucial for comprehensive patient assessment. The medication history helps identify potential triggers. Prior psoriasis history is important because approximately 50% of GPP patients have background plaque psoriasis, although absence doesn't rule out GPP, but presence supports it. The distribution, morphology, and time course provide essential diagnostic clues.

Let's examine our patient carefully. Your examination reveals a widespread erythema studded with numerous pustules on an inflamed background. The pustules are distributed across the trunk, extremities, and body folds. Importantly, they're not restricted to acral areas or within pre-existing plaques, which is consistent with the IPC essential criterion for GPP. While you find no obvious psoriatic plaques, you do notice subtle nail changes, mild pitting of several fingernails, which can be an early sign of psoriatic disease. Some areas are already showing early desquamation. The patient is febrile, tachycardic, and markedly uncomfortable.

At this point, the differential diagnosis includes both GPP and AGEP, though the timing, symptoms beginning 11 days after completing antibiotics, would be atypical for AGEP which usually presents within 1 to 11 days of starting medication. The family history of psoriasis and subtle nail findings are clues worth noting. A comprehensive patient assessment is fundamental to accurate diagnosis. It has four key components.

First, clinical history. Ask about personal and family history of psoriasis, because approximately 50% of GPP patients have background plaque psoriasis. Document medication exposure carefully, including timing and sequence. Identify potential triggers, like infections or pregnancy.

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Second, physical examination. Carefully characterize pustule morphology and distribution. Look for pre-existing plaques, assess nail changes, and evaluate for acral involvement.

Third, laboratory evaluation. Check for neutrophilia, elevated inflammatory markers, and metabolic abnormalities like hypocalcemia and hypoalbuminemia, which are common in GPP.

Fourth, diagnostic testing. Skin biopsy is essential for histopathology. Direct immunofluorescence can exclude other blistering conditions, and genetic testing may be valuable when GPP is suspected.

This systematic approach ensures you gather all the information needed for an accurate diagnosis.

Let's see our patient's test results. The laboratory results show marked neutrophilia at 85% and significantly elevated inflammatory markers, findings consistent with severe pustular inflammation. Critically, notice the eosinophil count, only 1% which is normal, not elevated. This is a clue that argues against AGEP. The low calcium and albumin levels suggest metabolic complications, which are common in severe GPP.

The skin biopsy is particularly revealing. The pathologist identifies characteristic spongiform pustules of Kogoj, the hallmark histopathologic feature of GPP, with neutrophilic infiltration and minimal eosinophils within the dermis. There's also acanthosis with elongated rete ridges supporting a psoriasiform process. Cultures are negative, confirming sterile pustules. These biopsy findings strongly favor GPP over AGEP, which typically shows prominent eosinophils. Combined with the atypical timing for an adverse drug reaction, GPP is moving to the top of our differential diagnosis.

When faced with acute pustular eruptions, several conditions enter your differential diagnosis. Generalized pustular psoriasis and acute generalized exanthematous pustulosis are the most challenging to differentiate. Other neutrophilic dermatoses include subcorneal pustular dermatosis, IgA pemphigus, palmoplantar pustulosis, and acrodermatitis continua of Hallopeau. Each has distinctive features. IgA pemphigus shows intracellular IgA deposits on direct immunofluorescence.

Subcorneal pustular dermatosis has a chronic relapsing course with annular patterns.

Our focus today is on GPP versus AGEP because they're the most commonly confused conditions with each other in acute presentations. Let's dive deeper into how we differentiate them.

This comparison table highlights the critical differences between GPP and AGEP. Pay close attention to several key distinguishers.

First, drug relationship. AGEP is strongly drug associated, over 90% of cases, with rapid onset, typically within 1 to 11 days after initiation of the medication. GPP can be drug triggered but doesn't follow this typical pattern.

Second, personal history. Approximately 50% of GPP patients have background plaque psoriasis, while AGEP patients typically have no psoriasis history.

Third, clinical course. AGEP resolves rapidly within 1 to 2 weeks after drug withdrawal, whereas GPP persists for weeks to months without specific treatment.

Fourth, histopathology. GPP shows characteristic spongiform pustules of Kogoj with minimal eosinophils, whereas AGEP shows prominent eosinophils within the dermis and eosinophilic spongiosis.

Fifth—and this is critical—IL36RN mutations are often found in GPP cases but are absent in AGEP.

Finally, peripheral eosinophilia is common in AGEP but rare in GPP.

Remember, IL36RN mutation plus Kogoj pustules strongly support GPP, whereas abundant eosinophils, both on histology and in the peripheral blood, plus rapid drug-related onset support a diagnosis of AGEP.

The International Psoriasis Council developed consensus diagnostic criteria for GPP in 2024. The essential criterion—the must-have finding—is macroscopically visible, sterile pustules on an erythematous base that are not restricted to acral areas or within existing psoriatic plaques. This is the foundation of diagnosis.

Supportive features include systemic symptoms like fever, laboratory abnormalities such as neutrophilia and elevated inflammatory markers, in addition to a personal history of psoriasis, which is present in about 1/2 of cases.

Skin biopsy is strongly recommended to confirm the diagnosis and distinguish GPP from conditions like AGEP. Look for spongiform pustules of Kogoj and minimal eosinophils. Direct immunofluorescence has limited value for GPP itself but can help exclude other blistering conditions like IgA pemphigus.

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Genetic testing for the interleukin 36RN gene and other mutations isn't required for diagnosis but, when positive, strongly confirms GPP and provides important pathogenic insights and therapy guidance. These criteria provide a standardized framework for GPP diagnosis.

The EuroSCAR validation score is a standardized tool to diagnose AGEP. It evaluates three categories: morphology, clinical course, and histopathology. Histopathology carries the most weight. The total score determines diagnostic certainty. Zero rules out AGEP; 1 to 4, AGEP is possible; 5 to 7, AGEP is probable; and 8 to 12, it's definite AGEP. This validated scoring system provides objective criteria for an AGEP diagnosis and helps standardize clinical practice and research. Let's apply IPC generalized pustular psoriasis criteria and EuroSCAR AGEP criteria to our patient.

Now let's synthesize the information. Our patient meets the IPC essential criterion for GPP, sterile pustules on background erythema not restricted to acral areas or plaques. He has multiple supportive features, fever, systemic symptoms, neutrophilia, elevated inflammatory markers, metabolic abnormalities, family history of psoriasis, subtle nail changes, and critically, characteristic spongiform pustules of Kogoj with minimal eosinophils on histology.

Now consider AGEP. The timing is atypical. Symptoms began 11 days after completing the antibiotic, outside the typical 1- to 11-day window for AGEP onset. His eosinophil count is normal, and histology shows minimal eosinophils. Both argue strongly against AGEP.

This patient has generalized pustular psoriasis. He meets the IPC essential criterion and has multiple supportive features.

Additional testing provides important context. Genetic testing for IL36RN mutations is negative in our patient. He has wild-type genes. This is actually expected to some degree. Remember, mutations are found in only 20 to 25% of GPP cases, meaning the majority of GPP patients have no identifiable IL36RN mutations. So negative genetic testing does not exclude GPP.

Now, let's discuss biomarkers. In GPP, the IL-36 pathway is markedly upregulated, regardless of mutation status. IL-36 alpha, beta, and gamma are central to the pathogenesis. Neutrophil chemokines like interleukin 8 are elevated along with neutrophil markers. If we tested this patient's serum, we'd expect to see elevated interleukin 36 gamma and interleukin 8 with normal eosinophilic markers, exactly what distinguishes GPP from AGEP. In AGEP, you see elevated eosinophilic markers, such as increased interleukin 5 and interleukin 13, with relatively lower interleukin 36 activation.

It's important to remember most biomarkers are research tools, not standard clinical tests. IL36RN genetic testing is available and valuable for confirming cases, but it takes significant time to get results, and a negative result doesn't rule out GPP. The majority of GPP cases are mutation negative.

In our patient, the clinical features, histopathology, and biomarker profile all support a diagnosis of GPP despite negative genetic testing.

Now that we've considered the diagnosis of GPP and our patient's presentation, let's connect these to what we know about the immunological drivers of GPP. Generalized pustular psoriasis is fundamentally an interleukin 36-driven disease. Keratinocytes release interleukin 36 alpha, beta, and gamma, which activate innate immune pathways and trigger downstream production of cytokines like interleukin 1 beta and interleukin 8. Interleukin 36Ra normally acts as the receptor antagonist, so when that function is reduced or absent, even without a detectable mutation, we see unopposed signaling and a surge in neutrophil-recruiting chemokines like interleukin 8.

Compared with plaque psoriasis, GPP shows a more dominant interleukin 1 and interleukin 36 axis and relatively less interleukin 17A activity, which helps explain why interleukin 17 inhibitors may be only partially effective. Emerging markers like TNFSF15, which is released by neutrophils, also amplify the keratinocyte neutrophil feedback loop.

Together, this cytokine profile reinforces what we observed in our patient: marked neutrophilia, elevated inflammatory markers, and a biopsy showing spongiform pustules. These immunologic signatures not only support the diagnosis but also guide our therapeutic approach as we move into targeted treatments.

This practical workflow provides a systemic approach to diagnose pustular dermatoses. Start with comprehensive history and examination. Document medication timing, prior psoriasis history, pustule characteristics, and systemic symptoms.

Move to laboratory evaluation. Check the complete blood count with differential to assess for neutrophilia and eosinophilia. Measure inflammatory markers, assess for metabolic abnormalities, and culture pustules to rule out infection.

Step three is essential, perform a skin biopsy. Histopathology differentiates Kogoj spongiform pustules in GPP from prominent eosinophils in AGEP. Direct immunofluorescence helps exclude other conditions like IgA pemphigus.

In step four, apply the diagnostic criteria we've discussed, IPC generalized pustular psoriasis criteria and the EuroSCAR AGEP score. These standardized tools provide objective frameworks for diagnosis.

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Finally, consider additional testing when appropriate. Genetic testing for interleukin 36RN when GPP is suspected, and biomarkers in research settings.

This systematic approach ensures comprehensive evaluation and accurate diagnosis leading to appropriate management.

Let's see how this applies to our patient. Our patient's final diagnosis is generalized pustular psoriasis. Multiple lines of evidence support this. He meets the IPC essential criterion with sterile pustules on erythema not restricted to acral areas or plaques. The histology shows characteristic spongiform pustules of Kogoj with minimal eosinophils and is diagnostic for GPP. He has key supportive features: fever, marked neutrophilia, elevated inflammatory markers, metabolic abnormalities, family history of psoriasis, and subtle nail changes. Evidence against AGEP includes the atypical timing, onset 11 days after completing the antibiotic, normal eosinophil counts, and minimal eosinophils on histology. After discontinuing the antibiotic and initiating targeted biologic therapy for GPP, the patient showed gradual improvement over 3 to 4 weeks, consistent with GPP's typical course, not the rapid resolution as typically seen in AGEP.

This case demonstrates that GPP can occur without interleukin 36RN mutations. In fact, the majority of GPP cases are mutation negative, and that systematic application of diagnostic criteria and careful histopathologic evaluation are essential for accurate diagnosis.

When diagnosing acute pustular eruptions, remember that timing, labs, and histopathology are critical. That's why, in practice, your first step should be to map out the medication timeline, order a CBC with differential, and secure a lesional skin biopsy early. Spongiform pustules of Kogoj and neutrophilia are diagnostic hallmarks of GPP, so use the IPC essential and supportive criteria systematically in every suspected case. Even when IL36RN mutations are absent, interleukin 36 dysregulation still drives GPP, so interpret labs and biopsy with this mechanism in mind. Consider genetic and biomarker testing when available while being mindful of turnaround times. And finally, once GPP is confirmed, initiate treatment promptly to stabilize the patient and prevent complications.

Let's move on to our final case, GPP management plan using targeted therapy. This module focuses on treatment of GPP. Over the next 10 to 12 minutes, you'll work through a case to develop your skills in evaluating targeted therapies and formulating comprehensive management plans.

Let's meet our patient, a 50-year-old postmenopausal woman presenting with a severe GPP exacerbation. She has widespread erythema and pustules covering more than 10% of her body surface area, high fever, severe fatigue, and intensely painful skin. This isn't her first episode. She has a history of recurrent GPP with three flares in the last 5 years, previously treated with acitretin and cyclosporine.

Here's the critical trigger history. Approximately 2 weeks ago, she developed an upper respiratory tract infection, bacterial sinusitis, for which she completed a short course of antibiotics. About 10 days ago, shortly after the infection onset, she began developing her current GPP flare. Infection is one of the most common and well-recognized triggers of GPP flares. Systemic infection activates innate immune pathways, which in genetically and/or immunologically predisposed individuals can dysregulate the interleukin 36 axis, triggering the neutrophil-driven cascade that characterizes GPP. The close temporal relationship between her upper respiratory infection and flare onset strongly implicates infection as the trigger here.

As we work through this case, you'll learn to assess severity, select appropriate targeted therapies, and develop a comprehensive long-term management plan.

The Generalized Pustular Psoriasis Physician Global Assessment, or GPPGA, is a validated 0 to 4 scale that assesses overall GPP severity by evaluating erythema, pustulation, and scaling/crusting across the entire body, with scores ranging from 0, or clear skin, to 4, which is severe disease. The total GPPGA score is calculated by averaging these three individual scores. It is used in clinical trials and clinical practice to guide treatment decisions and monitor disease activity during acute flares.

Let's assess the severity of this flare using the GPPGA score. For our patient, let's evaluate. Erythema: she has widespread, deep, fiery red erythema, so that's a score of 4. Pustules: high density with pustular lakes, pustules covering more than 10% of her body surface area, so that's also a 4. Scaling and crusting: moderate. Scaling is beginning to develop, covering most lesions, so that's a 3. Now, calculate 4 plus 4 plus 3 equals 11, divided by 3 equals approximately 3.7. So according to GPPGA scoring rules, if the mean is 3.5 or higher, the total GPPGA score is 4, indicating severe disease. So our patient has a score of 4, or a severe GPP flare.

Before discussing targeted interleukin 36 therapies, let's review the historical treatment landscape for GPP. Traditionally, systemic agents like acitretin, cyclosporine, and methotrexate were first-line options. Acitretin showed the highest efficacy but has significant dose-dependent adverse events, including teratogenic effects and lipid abnormalities.

Biologics developed for plaque psoriasis, such as TNF alpha, interleukin 17, and interleukin 23 inhibitors, have shown variable efficacy

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in GPP, with complete remission rates ranging from 42 to 62% for TNF alpha and interleukin 17 inhibitors, but lower rates for interleukin 23 inhibitors.

A 2021 survey of dermatologists revealed critical gaps in GPP; 67% considered available treatments inadequate in preventing flares, 72% found them too slow to control acute flares, and 83% reported patients had residual symptoms between flares despite using the full range of available therapies. These findings highlighted the urgent need for fast-acting, long lasting GPP-specific treatments, which led to the development of interleukin 36 receptor inhibitors.

Now let's discuss spesolimab, the first targeted therapy specifically approved for GPP. Spesolimab is a humanized monoclonal antibody that specifically binds to the interleukin 36 receptor. And by binding to the interleukin 36 receptor, spesolimab blocks all three interleukin 36 cytokines alpha, beta, and gamma from binding and activating the receptor. This prevents interleukin 36 signaling, which inhibits the downstream cascade of chemokine production, neutrophil recruitment, and keratinocyte activation.

Remember from previous learning, the interleukin 36 pathway dysregulation drives GPP pathogenesis. Unopposed interleukin 36 signaling triggers the amplification loop that produces the pustules. So by directly targeting the interleukin 36 receptor, spesolimab interrupts this core pathogenic mechanism at its source. This is why spesolimab is so effective. It addresses the fundamental immunological driver of GPP, not just downstream inflammation.

In September 2022, spesolimab became the first FDA approved therapy specifically indicated for GPP. Let's review the clinical trial evidence supporting its use.

The Effisayil 1 trial was a pivotal phase 2 randomized trial evaluating spesolimab for acute GPP flares. Fifty-three patients experiencing active flares were randomized in a 2:1 fashion to receive either a single intravenous dose of 900 mg of spesolimab or placebo. The primary endpoint was achieving a GPPGA pustulation subscore of 0, meaning no visible pustules, at week 1. The key secondary endpoint was achieving a GPPGA total score of 0 or 1, implying clear or almost clear skin, also at week 1.

The results were striking. At the end of week 1, 54% of patients in the spesolimab group achieved complete pustular clearance compared to only 6% in the placebo group, a statistically significant difference with a P value of less than 0.001. For the secondary endpoint, 43% of spesolimab-treated patients had clear or almost clear skin versus 11% treated with placebo, also statistically significant results. These results demonstrated that spesolimab produces rapid, clinically meaningful improvement in acute GPP flares within just 1 week, addressing the critical unmet need for a fast-acting, effective therapy. Spesolimab was generally well tolerated, with an increased risk of infections, anti-drug antibodies, and systemic symptoms compared to placebo.

The Effisayil 2 trial evaluated subcutaneous spesolimab for preventing GPP flares, addressing the long-term management need. This phase 2b trial randomized 123 patients to one of three doses of subcutaneous spesolimab or placebo, with a primary endpoint of time to first flare by week 48. The high-dose spesolimab regimen consisted of a 600 mg loading dose followed by 300 mg every 4 weeks.

By week 48, the results showed a clear dose response relationship. Only 10% of patients in the high-dose spesolimab group experienced a flare compared to 29% in the medium dose, 23% in the low dose, and 52% in the placebo group. High-dose subcutaneous spesolimab was statistically superior to placebo in preventing GPP flares. The safety profile was favorable, with infection rates similar across all treatment arms. These results demonstrated that subcutaneous spesolimab maintenance therapy can effectively prevent GPP flares over the long term, filling a critical gap identified in the 2021 survey where 67% of dermatologists felt available treatments were inadequate for flare prevention.

Spesolimab received FDA approval in September 2022 for treatment of GPP flares in adults with intravenous dosing of 900 mg as a single infusion. In March 2024, the FDA expanded approval significantly, a pediatric expansion to patients 12 years old and older weighing at least 40 kg, subcutaneous formulation approval, and extension to prevention indication for maintenance therapy.

The current dosing depends on indication. For acute flares, 900 mg intravenously as a single infusion over 90 minutes, which may be repeated once at week 1 if symptoms persist. For flare prevention, subcutaneous dosing consists of a 600-mg loading dose administered as four 150-mg injections, followed by 300 mg every 4 weeks. If a patient receives IV spesolimab for an acute flare and then transitions to maintenance, they start 300 mg subcutaneously every 4 weeks beginning 4 weeks after the IV dose, with no loading dose needed.

Let's discuss imsidolimab, an emerging interleukin 36 receptor inhibitor in the pipeline for GPP. Imsidolimab is a humanized IgG4 monoclonal antibody that targets the interleukin 36 receptor, similar to spesolimab. It blocks interleukin 36 alpha, beta, and gamma signaling, antagonizing interleukin 36 pathway activation.

Phase 3 trials assessed 750 mg and 300 mg imsidolimab for achieving GPPGA and Pustulation Rating Scale, or PRS, scores of 0 or 1 after 4 weeks. Fifty-three percent of patients on both doses of imsidolimab achieved GPPGA scores of 0 or 1, and 40% in the 750-mg

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group, and 67% in the 300-mg group achieved a PRS of 0 compared to 13% for placebo. Adverse effects were mild.

Now let's apply what we've learned. Our patient has severe GPP with a GPPGA score of 4, more than 10% body surface area involvement, fever, systemic symptoms, and a history of recurrent flares. Which treatment approach is most appropriate? She needs rapid control of this acute, severe flare, and she has a history of recurrent disease requiring long-term prevention. Think about the evidence we just reviewed from Effisayil 1 and 2. Which treatment approach is the most appropriate for this patient?

The correct answer is C, administer spesolimab 900 mg IV for acute flare, then transition to subcutaneous maintenance. For severe, acute GPP flares, implying a GPPGA score of 4 with greater than 10% body surface area and systemic symptoms, spesolimab 900 mg IV is indicated for rapid control. The Effisayil 1 trial showed 54% of patients achieved pustular clearance within 1 week. Given our patient's history of recurrent flares, she's also a candidate for subcutaneous maintenance therapy, 300 mg every 4 weeks thereafter, starting 4 weeks after IV treatment, to prevent future flares. This addresses both acute management and long-term prevention.

Choice A, acitretin. Acitretin is a traditional systemic option but it has a slower onset than spesolimab, and it's inadequate for severe acute flares requiring rapid control. Choice B, topical steroids. Topical therapy alone is insufficient for severe GPP with systemic symptoms. This patient requires systemic therapy. Choice D, cyclosporine. While cyclosporine can be effective, spesolimab provides more rapid targeted therapy specifically for GPP. Given our patient's recurrent flares, she also needs long-term prevention strategies.

Let's see how our patient responded. She received spesolimab 900 mg intravenously. At week 1 of follow-up, the improvement is dramatic. Clinically, pustulation is markedly improved with only a few residual pustules. Erythema is significantly reduced. There's minimal new scaling. Fever is completely resolved, and the patient reports substantial reduction in pain and fatigue.

Let's reassess her GPPGA score. Erythema is now mild, score of 2, improved from 4. Pustules are almost clear with rare visible pustules, which implies a score of 1, which is also improved from 4. Scaling is minimal now, a score of 1, which is improved from 3 at baseline. The new GPPGA total score is 2 plus 1 plus 1 divided by 3, which equals 1.33 and gives a GPPGA total score of 1, meaning her skin is almost clear.

Her laboratory values normalized. Now her white blood cell count is normal, and CRP decreased from 142 to 18. This represents an excellent response, achieving almost clear skin within 1 week and is consistent with the Effisayil 1 trial results.

Now we need to develop a long-term management plan.

The three treatment goals of GPP are to control current flares which we've achieved with IV spesolimab, prevent or minimize future flares which is our focus now, and optimize quality of life. Given our patient's history of recurrent GPP with three prior flares over the last 5 years, her excellent response to IV spesolimab and her high risk for future flares, the recommended plan is to transition to subcutaneous spesolimab maintenance therapy. At week 5, which is 4 weeks after IV dose, we initiate subcutaneous spesolimab 300 mg which is given as two 150-mg injections. She then continues 300 mg subcutaneously every 4 weeks thereafter. Importantly, no loading dose is needed since she received 900 mg IV treatment for the acute flare. This addresses her recurrent disease pattern with convenient subcutaneous administration. If she does experience a flare while on maintenance therapy, which is uncommon, she can be treated with spesolimab 900 mg intravenously and then resume subcutaneous dosing.

Let's also consider quality of life assessment. The Dermatology Life Quality Index, or DLQI, is a validated tool to assess this. It's a 10-question questionnaire that evaluates the impact of skin disease over the past week, with scores ranging from 0 to 30. Higher scores indicate greater negative impact on quality of life. Research shows GPP causes significantly worse quality of life compared to plaque psoriasis. The most common problems reported by GPP patients include itchy, painful, stinging skin, fatigue, treatment burden, and impacts on work, daily activities, and emotional wellbeing. We should assess DLQI at baseline, during flares, and while on maintenance therapy, with a goal of improvement reflecting effective flare control and prevention.

Our patient's baseline DLQI score was 22, indicating a very large effect on quality of life. By week 12 on maintenance therapy, her DLQI improved to 4, a small effect on quality of life, demonstrating treatment success for quality of life with spesolimab beyond just the clinical measures.

Let's summarize the key teaching points. First, targeted interleukin 36 receptor inhibition is transformative for GPP. Spesolimab specifically blocks the interleukin 36 receptor, preventing the core pathogenic mechanism. It's the first FDA-approved therapy specifically for GPP and addresses critical unmet needs, rapid action for acute flares, and long-term prevention. Clinical trial Effisayil 1 data showed 54% pustular clearance versus only 6% with placebo at week 1 for acute flares. Effisayil 2 demonstrated a 10% flare rate versus 52% with placebo for maintenance prevention. Spesolimab is superior to historical options, including traditional systemic medications and non GPP specific biologics.

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Second, comprehensive management requires assessing severity with GPPGA scoring, treating acute flares with spesolimab 900 mg IV for rapid control, providing long-term maintenance with subcutaneous spesolimab 300 mg every 4 weeks, and monitoring quality of life using the DLQI. Individualize treatment plans by considering flare frequency, severity, triggers, and patient preference. Patients with recurrent flares should receive maintenance therapy. Always address systemic symptoms and metabolic complications. Emerging therapies like imsidolimab will likely soon expand options.

The bottom line, interleukin 36 receptor inhibitors have revolutionized GPP treatment, providing both rapid flare control and effective long-term prevention with a favorable safety profile.

Thank you for joining me in this activity, and I hope you can apply this knowledge in your everyday practice. Please complete the evaluation and claim continuing education credit.

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