Advances in Pemphigus and Pemphigoid: A Report of the International Meeting of the Pemphigus and Pemphigoid Foundation in Thessaloniki, Greece

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The International Meeting of the International Pemphigus and Pemphigoid Foundation (IPPF) was held at Thessaloniki, Greece, on August 29−31, 2024. Members of the steering committee were Patrick Dunn, Dedee F. Murrell, Aimee Payne, Enno Schmidt, Victoria Werth, Marc Yale, and Jun Yamagami and the overall meeting organizer, Aikaterini Patsatsi (Figure 1).

The overall goal was to present new developments in basic research and translational and clinical studies, to present management updates for pemphigus and pemphigoid

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Abbreviations: AIBD, autoimmune blistering disease; BP, bullous pemphigoid; CAART, chimeric autoantigen receptor T; DIF, direct immunofluorescence; DSG, desmoglein; EBA, epidermolysis bullosa acquisita; FDA, Food and Drug Administration; IGA, Investigator Global Assessment; IPPF, International Pemphigus and Pemphigoid Foundation; IVIG, intravenous Ig; LAD, linear IgA dermatosis; MMP, mucous membrane pemphigoid; OLP, oral lichen planus; PDAI, Pemphigus Disease Area Index; Th, T helper; Treg, regulatory T cell

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diseases, to address how to improve the design of more robust and practical relevant clinical trials, to highlight the importance of patients' organizations and of patients' unmet needs and perspectives, and to highlight the gaps of knowledge for future research endevors (Figure 2).

FROM PEMPHIX TO PEMPHIGUS

Genetics of pemphigus vulgaris

Eli Sprecher (Tel Aviv Sourasky Medical Center, Israel) presented a survey of various genetic association studies, including gene association studies, GWASs, next-generation sequencing, and RNA sequencing, to explore the genetic and ethnic predisposition in pemphigus vulgaris. He emphasized the crucial role of 2 genes carrying risk variants for pemphigus vulgaris—*ST18* and *TRAV19*—whose dysfunction leads to increased TNFα and IL-17 expression. Variants in those 2 genes predict a more severe disease. He further noted that these genetic association studies may pave the way for new therapeutic targets.

Pathogenesis of pemphigus

Franziska Vielmuth et coll (Ludwig-Maximilians-University, Munich, Germany) performed an analysis of the molecular pathogenesis of pemphigus, focusing on the critical roles of adhesion molecules and autoantibodies to better dissect the mechanisms that contribute to the adhesive strength of desmogleins (DSGs) in pemphigus vulgaris. A better understanding of the specific signaling pathways activated by autoantibodies and of the phenomenon of hyperadhesion in pemphigus vulgaris is important to identifying druggable targets and to developing future therapeutic strategies. She highlighted that apremilast effectively prevents IgG-induced loss of intercellular adhesion in pemphigus vulgaris ex vivo in human skin and in vitro and in vivo in mice by increasing cAMP levels.

Autoreactive B cells in pemphigus

Jun Yamagami (Tokyo Women's Medical University, Japan) presented his research on the detailed characterization of DSG-specific B cells in patients with pemphigus. He demonstrated the development of a system for sorting DSG-specific B cells and performing RNA sequencing on these cells. By comparing gene expression in DSG-specific B cells before with those after treatment, he found suppression of B-cell activation pathways, correlating with the clinical course of the disease. RNA-sequencing results also indicated an upregulation of *CD137L*, a molecule potentially important for T-cell activation, in DSG-specific B cells. This suggests that these cells may play a role not only in autoantibody production but also in T-cell activation, offering insights into potential new therapeutic targets aimed at these specific cells.

Fogo selvagem (endemic pemphigus foliaceus)

Valeria Aoki (University of São Paulo Medical School, São Paulo, Brazil) shared her extensive experience in the field of pemphigus epidemiology in Brazil, focusing on the endemic form known as fogo selvagem. Molecular studies have identified the specific binding sites of autoantibodies in the extracellular domains of DSG1, particularly at the EC1 epitope. She emphasized that chronic exposure to insect bites, from parasites such as *Leishmania* and *Trypanosoma*, may trigger this form of pemphigus through antigen mimicry. Valeria Aoki also stressed the importance of avoiding anti-*Leishmania* vaccines in regions such as Tunisia and Brazil, where this phenomenon has been observed, because these vaccines could potentially induce this severe autoimmune disease.

The glycan theory of autoimmunity and glycan alterations in pemphigus

Emanuel Maverakis (University of California, Davis) presented his extensive research on the glycome and the glycan



Figure 1. Speakers at the 2024 IPPF Meeting in Thessaloniki, Greece. IPPF, International Pemphigus and Pemphigoid Foundation.



Figure 2. Scientific session at 2024 IPPF International Meeting. IPPF, International Pemphigus and Pemphigoid Foundation.

theory of autoimmunity, which he developed at University of California, Davis. According to this theory, each autoimmune disease is characterized by a unique glycan signature that drives its pathophysiology, and reversing these pathogenic glycan alterations could offer therapeutic benefits. His research has demonstrated that glycans serve as valuable biomarkers for human disease, age, and sex and likely play a critical role in the pathophysiology of autoimmune disorders by correlating with disease severity. In pemphigus, dominant glycans such as IgG4 3410 and IgG1 3410 have been identified in serum, with glycan alterations negatively associated with disease severity. He explained that their current strategy is to reverse pathological glycosylation by administering monosaccharide supplements to patients—a therapeutic approach known as monosaccharide feeding to treat immunobullous diseases.

Large-scale autoantibody profiling identifies actionable biomarkers linked to multiple disease parameters that can be used in predictive machine learning algorithms

Animesh A. Sinha (University at Buffalo, NY) presented a study demonstrating the presence of multiple autoantibody profiles in pemphigus vulgaris, including both anti-DSG and anti—non-DSG antibodies. He explained that *HLA* genetics play a crucial role in shaping the autoantibody response, which can be used to classify and predict different patient subgroups. These autoantibody profiles not only help to explain the clinical heterogeneity of the disease but also hold promise for the development of future individualized therapies.

The best way to use rituximab in pemphigus vulgaris and foliaceus

Pascal Joly (Rouen University Hospital, Rouen, France) presented the comprehensive development of rituximab as a standard treatment for pemphigus vulgaris. He explained that rituximab was initially used to treat severe, recalcitrant cases of pemphigus, showing greater efficacy when administered early. However, some patients required maintenance therapy owing to the increasing risk of relapse over time. Rituximab has since become the first-line therapy for pemphigus. A recent study demonstrated its long-term effects, with remissions lasting up to 7 years without the need for steroids, using a regimen of 2 g of rituximab at baseline, followed by 500 mg at months 12 and 18. Future research aims to develop personalized maintenance strategies on the basis of biomarker evolution, enabling the identification of patients with subclinical disease activity who are at high risk of relapse, so that they can be treated pre-emptively to prevent relapse. Pascal Joly also discussed several cases where the use of rituximab posed uncertainties and posed questions to the audience, including the role of intravenous Ig (IVIG) in rituximab therapy; the optimal timing and sequence between rituximab and IVIG; whether rituximab could be combined with plasmapheresis or immunoadsorption; the best treatment options for persistent rituximab nonresponders; and whether rituximab should be used as a first-line therapy in mild pemphigus or pemphigus foliaceus, especially in patients hesitant to be revaccinated for COVID.

FcRn inhibitors for pemphigus

Dedee Murrell (University of New South Wales, Sydney, Australia) presented the significance of *FcRn* transmembrane proteins, which bind to IgG and protect it from degradation by redirecting IgG away from lysosomes and recycling it to the cell surface. This process extends the half-life of IgG. Inhibiting *FcRn* presents a potential therapeutic target for treating various inflammatory and autoimmune diseases. Because pathogenic autoantibodies play a crucial role in many autoimmune conditions, reducing serum IgG could be an effective treatment. *FcRn* inhibitors, by specifically lowering IgG levels, are particularly promising for treating IgG autoantibody—driven diseases. She also noted that *FcRn* inhibition has been shown to be effective in preclinical models of autoantibody-driven disorders, such as myasthenia gravis. Dedee Murrell then presented results from a phase 2

open-label clinical trial of efgartigimod in patients with mild-to-moderate pemphigus vulgaris and pemphigus foliaceus. The trial indicated that *FcRn* inhibitors may rapidly reduce IgG and DSG antibodies in serum, with doses of 10—25 mg/kg weekly inducing a rapid effect.

DSG-chimeric autoantibody receptor T molecular and correlative profiling: lessons from a first-in-human study

Aimee Payne (Columbia University Irving Medical Center, New York, NY) presented findings from a phase 1 open-label safety and dosing study of autologous DSG3 chimeric autoantibody receptor T (CAART) cells (DSG3-CAART) in patients with active mucosal pemphigus vulgaris (NCT04422912). The study has enrolled 26 participants across dose-escalation cohorts as well as cohorts including preconditioning with IVIG and cyclophosphamide, with or without fludarabine, and multiple infusions. The study has not shown a consistent pattern of effect on clinical or serologic outcomes in treated participants. She presented translational data from participants' blood samples after DSG3-CAART infusion, which showed minimal- to low-level induction of IFNγ, combined with an increase in DSG3-CAART naïve or stem cell memory-like immunophenotypes. Collectively, these data indicate that DSG3-CAART is not activated after infusion, which may be due to inhibition by soluble anti-DSG3 antibodies and/or the rarity of anti-DSG3 target cells in patients. Future work will compare the single-cell profiles of DSG3-CAART before with those after infusion, examine strategies for reducing soluble autoantibodies, and evaluate the safety and efficacy of a global but transient B-cell depletion approach that aims to achieve immune reset using anti-CD19 CAART cells in subjects with mucosal or mucocutaneous pemphigus vulgaris.

Fas ligand inhibitors

Carlo Pincelli (University of Modena and Reggio Emilia, Milan, Italy) presented PC111, a human anti—Fas ligand mAb, as a novel, targeted therapy for the non-immunosuppressive treatment of pemphigus. PC111 has shown effectiveness in preventing FasL-dependent acantholysis of normal human keratinocytes in a dose-dependent manner. In a new ex vivo pemphigus model, PC111 was able to significantly reduce blister formation by 50—90%. In vivo studies using a proprietary transgenic humanized FasL mouse model further confirmed the efficacy of PC111 in blocking blister formation. However, further human studies are yet to be planned and designed.

Autoreactive T cells and their potential role in the treatment of pemphigus

Michael Hertl (University of Marburg, Germany) discussed the role of T helper (Th)2 and Th17 cells in the pathogenesis of pemphigus and reviewed studies analyzing the proinflammatory signatures in pemphigus vulgaris. He also examined the role of regulatory T cells (Tregs) in pemphigus, highlighting data that support the notion that B-cell depletion with rituximab can also reduce autoreactive T cells. Furthermore, he presented research on targeting T cells using DSG3 peptide-loaded nanoparticles in a phase 1 trial. This approach leverages immune tolerance mechanisms in the liver, aiming to alter immunological parameters and reprogram T-cell responses. The research suggests that this method can lead to changes in T-cell and B-cell activity as well as autoantibody levels. However, a dose—response relationship between DSG3-loaded nanoparticles and therapeutic outcomes needs to be established.

FROM PEMPHIX TO PEMPHIGOID DISEASES: INVITED LECTURES

Pathophysiology of bullous pemphigoid

Christoph Hammers (Regensburg University, Regensburg Germany and University of Lübeck, Germany) presented on clinical presentation, diagnostic parameters, and the current concept of the pathophysiology of bullous pemphigoid (BP). He described the complex mechanisms underlying the disease, which include the secretion of ILs (IL-6, IL-4, IL-13, and IL-8) from keratinocytes, the accumulation of inflammatory cells in the dermis, and FcR-dependent inflammatory processes involving anaphylatoxins, mast cell degranulation, and the attraction of neutrophils and eosinophils. Christoph Hammers also reviewed ongoing clinical studies in phases 1, 2, and 3 that are investigating new biologics and targeted therapies for BP. He noted that significant progress has been made over the last 5 decades in understanding the disease's complex pathophysiology. He discussed the impact of genetic, environmental, and biological factors on the development of BP. Current clinical trials are advancing our understanding of the disease, particularly regarding the Th2 microenvironment and the putative role of dermal fibroblasts. In addition, Christoph Hammers presented not-yet-published experimental data from his laboratory on the role of the complement system in the induction of BP. He then highlighted published data on impaired Treg function in the disease and that low-dose IL-2 treatment may help expand Tregs and improve disease control.

Pathophysiology of pemphigoid diseases other than BP

Enno Schmidt (University of Lübeck, Germany) discussed the complex pathophysiology of pemphigoid diseases. He highlighted that novel mouse models of mucous membrane pemphigoid (MMP) reflect major clinical and immunopathological characteristics of the human disease. These models are valuable for exploring key inflammatory mediators and evaluating novel therapeutic strategies. In addition, he noted that standardized diagnostic assays for serum IgG against laminin beta 4 are now available for anti-p200 pemphigoid, which will greatly facilitate diagnosis. Laminin beta 4, a newly identified component of the cutaneous basement membrane zone, likely exists as laminin 342. The pathogenic relevance of anti—laminin beta 4 and anti—laminin gamma 1 needs further investigation in vivo. IgM pemphigoid may present as a clinically and immunopathologically distinct entity, and additional cases are needed to confirm this hypothesis.

Association of BP with neurologic disease

Kaisa Tasanen (University of Oulu and Oulu University Hospital, Finland) presented epidemiological data from the National Health Register in Finland on the association between BP and neurologic and psychiatric diseases. The hypothesis under investigation was that neuroinflammation might trigger a cross-reactive immune response involving

both neural and cutaneous antigens. Autoantibodies against BP 180 have been observed in some neurodegenerative diseases; however, these autoantibodies do not bind to the cutaneous basement membrane. In addition, medications used to treat neurologic and psychiatric conditions may increase the risk of developing BP. Kaisa Tasanen also discussed the specific clinical and immunological characteristics of gliptin-associated BP. In such cases, treatment decisions depend on the severity of BP, with the safest approach being to discontinue gliptin medication for all affected patients.

Novel developments in the diagnosis of autoimmune blistering disease

Nina Van Beek (Universität zu Lübeck, Lübeck, Germany) presented the latest advancements in diagnosing autoimmune blistering diseases (AIBDs). Direct immunofluorescence (DIF) remains the gold standard for AIBD diagnosis. A key highlight of her talk was the introduction of new biochips for performing indirect immunofluorescence, which can now include up to 12 antigens. She emphasized the importance of the biopsy site when performing DIF: typically, a perilesional biopsy is needed, but for oral diseases, nonperilesional buccal biopsies are equally effective and more practical than perilesional buccal biopsies. In MMP with esophageal involvement, oral and skin biopsies are more sensitive than esophageal samples. Nina Van Beek also discussed recent studies suggesting that alpha-6 beta-4 integrin may be a relevant serological marker in MMP, although further investigation is needed. She noted that artificial intelligence will likely enhance and accelerate diagnostics in the future. Combining traditional diagnostic tools with biomarker assessments could enable more individualized treatment approaches, leading to improved outcomes. The diagnostic criteria for all AIBDs outlined in the guidelines should make AIBD diagnosis more accessible for all dermatologists.

PEMPHIGOID DISEASES: TREATMENT UPDATE

Unmet needs in patients with pemphigoid diseases: current gaps

Luca Borradori (Inselspital, Bern, Switzerland) emphasized the major objectives in the management of pemphigoid diseases: to make an accurate diagnosis without delay, to control and heal the mucocutaneous lesions or prevent progression, to improve patients' QOL, to minimize the side effects of the used therapies, and to maintain remission. This group of diseases almost invariably affects elderly patients in reduced general condition, with multiple comorbidities. These patients often have fear and anxiety and sometimes show an impaired cognitive function. There are important practical gaps in their management. Effective and safe therapies for both the middle- and long-term control of pemphigoids are missing. Corticosteroids and immunosuppressants may have severe side effects and/or contraindications and often result in unsatisfactory responses, with need of maintenance therapies, high relapse rates, and practical constraints related to their administration and need of regular laboratory examinations. Furthermore, studies have failed to show significant improvements in patients' QOL, even when remission is achieved. Therefore, when treating patients with skin diseases, it is essential to focus on what truly matters to them. The validated Patient-Reported Impact of Dermatological Diseases measure, which has been developed under the leadership of Globalskin (International Alliance of Dermatology Patient Organizations), employs robust psychometric methods to properly assess the physical, psychological, and social of dermatological diseases on patients' life. Physicians should carefully listen to their patients; understand their needs; as well as provide information about the disease in clear, understandable terms. Treatment options, along with their advantages and side effects, should be discussed openly. Patients should be empowered to make their own medical decision.

Emerging therapies for MMP, linear IgA dermatosis, and epidermolysis bullosa acquisita

Frédéric Caux (Avicenne Hospital, Paris, France) presented the European guidelines for the treatment of MMP and discussed clinical trials involving rituximab for MMP. Currently, a randomized double-blind clinical trial is underway in France (NCT03295383) to compare rituximab with cyclophosphamide, because it remains unclear whether rituximab demonstrates superior efficacy. Rituximab still requires formal evaluation for MMP and other subepidermal autoimmune bullous diseases. Frédéric Caux also discussed the use of dupilumab, along with cases and trials involving Jak inhibitors (baricitinib, tofacitinib, abrocitinib) for MMP. He then introduced the European guidelines for the treatment of linear IgA dermatosis (LAD), noting that IgA epidermolysis bullosa acquisita (EBA) has been excluded from the LAD group and is now categorized within the EBA group. He presented cases of dupilumab use and introduced CD89 inhibitor JJP-1212 for a potential future treatment of LAD. In addition, Frédéric Caux highlighted the International Bullous Diseases Group's consensus on EBA, pointing out that to date, no treatment recommendations have been discussed in the European guidelines for EBA, which he identified as a significant gap that needs to be addressed in the near future. He presented and analyzed cases involving Jak inhibitors and dupilumab for EBA. Overall, dupilumab is currently being evaluated in an industry clinical trial for BP, and Frédéric Caux emphasized that industry-sponsored clinical trials for other pemphigoid diseases could be beneficial and should be designed to address these conditions.

Dupilumab in BP: what's the evidence?

Meng Pan (Department of Dermatology, Rui Jin Hospital, Shanghai, China) presented a comprehensive single-cell RNA analysis demonstrating a Th2 cell predominance in BP as well as elevated levels of type 2 inflammatory cytokines. The local immune microenvironment within BP lesions is characterized by a complex interaction between various immune cells. Amplified Th2 cells in these lesions express type 2 inflammatory cytokines and exhibit a T peripheral helper cell phenotype, which promotes B-cell differentiation into plasma cells. The aggregation and activation of Th2 cells are supported by several chemokines, with mast cells, C1q+ macrophages, and NLRP3+ macrophages playing key roles in driving Th2 infiltration and activation. Mast cells in BP lesions are particularly active, aiding in the recruitment of additional Th2 cells. Typical BP features, such as intense pruritus, an urticarial prodrome, peripheral eosinophilia, elevated IgE, and expanding evidence from both in vitro and in vivo studies, point to type 2 inflammation as a significant driver of BP pathogenesis. This suggests that targeting the

effectors of type 2 inflammation may offer novel and effective treatment approaches for BP. Dupilumab has been shown to significantly alleviate clinical and serological indicators in BP patients. In a retrospective cohort study, dupilumab treatment led to an improvement in clinical symptoms, with most symptoms controlled within 2 weeks, and antibody titers significantly decreased after 4 months. The safety profile of dupilumab was favorable, although concurrent infections and eosinophilia may present potential concerns.

The role of anti-IgE treatment

Janet Fairley (University of Iowa, Iowa City, IA) presented her extensive research on the role of IgE in BP. She also shared cases of BP successfully treated with omalizumab, suggesting the possibility of distinct BP endotypes—variations that may explain why some patients respond well to anti-IgE treatment, whereas others do not. Omalizumab appears to benefit BP either as monotherapy or as a steroid-sparing agent, with patient responses occurring independently of total IgE levels. Notably, IgE levels cannot be used to guide therapy after the initial use of omalizumab because it paradoxically results in the prolonged circulation of free IgE. Moreover, not all anti-IgE treatments, such as ligelizumab and quilizumab, have shown the same efficacy in patients with asthma and chronic urticaria. Given this, pharmaceutical companies are unlikely to support trials for a small number of patients with BP if these drugs are not successful in treating asthma or urticaria.

OPTIMAL DESIGNS FOR BP AND PEMPHIGUS STUDIES: DISCUSSION ON CLINICAL TRIAL ENDPOINTS

Lessons about optimal designs for BP and pemphigus studies: approved endpoints for clinical trials, a comparison of autoimmune diseases

Victoria Werth (Philadelphia VA Hospital, Philadelphia, PA) presented a comprehensive overview of studies on AIBD conducted over the past 2 decades. Although numerous studies have investigated disease mechanisms, only 1 drug—rituximab for pemphigus vulgaris—has been approved. She emphasized that trial design, recruitment, and logistical challenges are major barriers to conducting successful trials for rare diseases such as AIBD. In these trials, the requirement for steroids (which can skew outcomes in the placebo group), the dynamic course of the disease, and the clinical heterogeneity of patients have contributed to failed trials, wasting efforts and resources (8 trials for BP and 17 for pemphigus). However, she stressed the importance of publishing these failed trials to build a knowledge base. In addition, primary endpoints in these trials are often too strict, and there is a need to redefine consensus endpoints, similar to the work done on modifying steroid doses. She highlighted that achieving stable disease with a daily intake of 10 mg of prednisolone should not be considered a successful outcome. Complete remission as a primary endpoint is overly stringent. Steroids act as confounders in the placebo group, so trial designs should consider enforced steroid tapering or no steroids for patients with milder or inactive disease. Victoria Werth also suggested re-evaluating secondary endpoints, such as total steroid dose, mean steroid dose, duration of complete remission, time to first complete remission, time to flare or relapse, number of relapses, and QOL measures. Recruitment challenges should be addressed by reconsidering the definition of moderate disease, including older patients in the placebo arm, and recognizing the burdens of travel and study visits for participants. Decentralized trials with home visits, teledermatology, travel funding, and simplified visit schedules could improve participation. To reduce the burden on investigators, simpler protocols should be implemented; unnecessary outcomes (such as blister counts) should be eliminated; and ethical considerations should be reexamined—such as avoiding compulsory steroid withdrawal, which could be life threatening. Successful trial designs have included early time points for certain drugs in early-phase trials and using changes in disease activity indices such as Pemphigus Disease Area Index (PDAI) and Bullous Pemphigoid Disease Area Index rather than requiring complete disease remission. The Food and Drug Administration (FDA) currently allows a minimum steroid dose of 10 mg/day of prednisolone, which Victoria Werth noted is too high, because the IPPF community has agreed on a lower dose of 0.1 mg/kg/day. She also pointed out that the Investigator Global Assessment (IGA) response is often insensitive and does not align well with meaningful outcomes for both patients and physicians because evidence shows that patients may be significantly happier even without being completely clear of lesions. Increasing sample sizes to achieve statistical significance is not feasible in rare diseases. Victoria Werth continued by citing successful trials in other autoimmune diseases, including myasthenia gravis, atopic dermatitis, lupus, and hidradenitis suppurativa, and shared her experience working in the lupus group for clinical trial design. She highlighted the exceptional work done by the IPPF, particularly the Patient-Focused Drug Development organized by Marc Yale. Finally, she proposed forming an FDA consortium, led by the IPPF, to continue discussions on AIBD trial designs and outcomes, engaging patients, academics, and industry stakeholders.

Pitfalls in trials of steroid alternatives for AIBD

Dedee Murrell (University of New South Wales, Sydney, Australia) emphasized that variations in steroid receptor levels among patients, which are typically not measured at baseline in clinical trials, can act as significant confounding factors in randomized controlled trial outcomes. She also highlighted the importance of considering compliance with steroid dosing because patients often self-dose and can easily obtain extra steroid supplies outside of the trial. This can create an incentive for patients to take additional steroids to avoid relapsing, thus ensuring their continued participation in the trial (and access to free treatment) because a relapse might disqualify them from the study. In addition, she stressed that trials should not penalize patients who drop out, for example, by ensuring their access to necessary medications such as rituximab even after exiting the trial. The use of photography in trials was also underlined as essential for validating inclusion criteria and documenting both affected and unaffected areas of the skin. Photos should be taken at each visit, uploaded for review, and cross-checked with PDAI or IGA scores. An independent, blinded review of these

photos at the end of the trial would further ensure objectivity and quality control in assessing the outcomes.

INTERESTING CASES FROM AROUND THE WORLD

Maryam Daneshpazhooh (Tehran University of Medical Sciences, Tehran, Iran) presented an intriguing case of IgA pemphigus in a patient with a history of myasthenia gravis. The patient did not respond well to treatments with steroids, dapsone, rituximab, IVIG, and colchicine but showed improvement with adalimumab, while still receiving 100 mg of dapsone and 10 mg of prednisolone.

Dipankar De (Postgraduate Institute of Medical Education and Research, Chandigarh, India) presented a series of interesting and rare cases of extraflexural pemphigus vegetans. Pemphigus vegetans overall constitutes <5% of pemphigus cases. He analyzed the heterogeneous clinical presentations, diagnostic challenges, and differences from pemphigus vulgaris.

Savas Yayli (Koc University Hospital, Istanbul, Turkey) presented a case of IgG/IgA pemphigus characterized by a rare pustular eruption, a notably uncommon bullous disease. He discussed the clinical presentation and diagnosis and highlighted the controversy surrounding whether this condition represents a heterogeneous disorder rather than a distinct disease. It was suggested that it might be a transitional phase along a spectrum from classical pemphigus to IgA pemphigus.

Hiroshi Koga (Kurume University, Fukuoka, Japan) presented a case of subcorneal pustular dermatosis–type IgA pemphigus with autoantibodies against DSG1 and 3 and desmocollin 1–3, initially misdiagnosed as Grover's disease. This patient was also found to have IgA-type multiple myeloma. Hiroshi Koga discussed another case of pemphigus vegetans with autoantibodies against DSG1 and desmocollin 3, which responded effectively to systemic treatment with prednisolone (20 mg per day) and topical steroids. He analyzed various studies on the pathogenicity of desmocollin 3 autoantibodies in pemphigus. These autoantibodies can be detected in rare pemphigus subtypes, including pemphigus herpetiformis, pemphigus vegetans, paraneoplastic pemphigus, and the subcorneal pustular dermatosis subtype.

Anisa Mosam (Nelson Mandela School of Medicine, Berea, South Africa) presented a case involving pemphigus and venous thromboembolism, along with an analysis of various studies on the risk of venous thromboembolism in patients with pemphigus vulgaris, including those treated with rituximab. She also discussed a case of pemphigus foliaceus with vegetative plaques and a rare case of BP with palmoplantar keratoderma.

Thomas Tull (St John's Institute of Dermatology, London, United Kingdom) presented a case of pemphigus vulgaris where complete B-cell depletion and improvement of skin lesions were achieved after intravenous rituximab treatment. However, the patient had refractory scalp lesions that were treated with intralesional rituximab, leading to ongoing complete remission. Initially, the patient had persistently elevated anti-DSG1 and anti-DSG3 autoantibodies, which decreased after successful treatment of the scalp lesions. This suggests that cutaneous resident B cells in the scalp may have been responsible for the circulating DSG antibodies. This case highlights that the skin can act as a niche for B-cell survival.

Farzan Solimani (Charité University Hospital, Berlin, Germany) presented a perplexing case of IgM pemphigoid, a condition where IgM alone is not typically associated with complement activation or blister formation. The existing literature on IgM pemphigoid lacks western blot analyses. In Solimani's case, western blot testing revealed the presence of IgM as well as IgG and IgA antibodies. DIF might have been negative for IgG and IgA owing to possible epitope saturation by IgM or high avidity of IgM. The existence of an IgM pemphigoid entity remains controversial. Many publications on IgM pemphigoid report blistering, which may actually be due to undetectable IgG. This suggests that IgM pemphigoid might be a variant of classical BP rather than a distinct entity. Farzan Solimani emphasized that comprehensive western blot images with full protein should be included in publications, and additional serological studies are needed to clarify this potential subform of BP.

Marwah Adly Saleh (Department of Dermatology, Cairo University, Giza, Egypt) presented a case of unilateral hand pustules and erosions in a female aged 57 years, which was diagnosed as dyshidrosiform pemphigus vulgaris. This diagnosis should be considered in patients with known pemphigus who experience disease relapse with dyshidrosiform lesions on the soles and hands. Differential diagnoses for blistering on the hands and feet include dyshidrosiform pemphigoid, dyshidrosiform lichen planus (LAD), and dyshidrosiform pemphigus vulgaris.

Maike Holtsche (Klinikum Oldenburg, Germany) presented a case of anti-p200 pemphigoid as a differential diagnosis for erythema multiforme majus/Fuchs syndrome, confirmed by the presence of laminin beta 4 in a biochip. Patients with anti-p200 pemphigoid typically require lower corticosteroid doses and shorter treatment durations. In this case, the initial ocular involvement improved rapidly, attributed to herpes simplex virus 1 infection and bacterial conjunctivitis. Significant improvement in skin and oral lesions was observed with azathioprine and prednisolone.

Donna Culton (University of North Carolina at Chapel Hill) discussed a case of MMP presenting as desquamative gingivitis initially misdiagnosed as oral lichen planus (OLP) owing to similar clinical features and lichenoid features on histopathology. She outlined the different treatment strategies for OLP and MMP as well as their distinct clinical, immunofluorescence, and histopathological features. Histopathological findings can be similar, which may be misleading, because ~18% of patients with MMP exhibit lichenoid features. Donna Culton reviewed several cases from the literature where MMP was diagnosed but presented lichenoid features clinically and histologically. She emphasized that lichenoid features in MMP can occur in other mucosal surfaces, such as ocular and genital areas. DIF is critical for accurate diagnosis, with a 95% sensitivity for MMP and only 66% for OLP. The vestibule is an excellent perilesional site for DIF when desquamative gingivitis is the only clinical finding. Differential diagnoses for desquamative gingivitis include OLP (36–75% of cases), MMP (9–46%), and pemphigus vulgaris (3–15%) when periodontal disease has been excluded.

CONCLUSIONS

The recent international meeting of the Pemphigus and Pemphigoid Foundation in Thessaloniki, Greece, marked a significant step forward in the understanding and management of these complex autoimmune diseases.

One of the primary areas of progress highlighted was the deepening understanding of molecular pathways involved in the pathogenesis of pemphigus and pemphigoid. This expanding knowledge offers new insights into how these diseases develop and, more importantly, opens up potential avenues for targeted therapies that could more precisely address disease mechanisms.

Nonetheless, the meeting also underscored ongoing unmet needs in treatment approaches, particularly the goal of achieving early control and sustained remission with reduced or no dependence on steroids. Developing therapies that minimize steroid use remains critical for patient QOL and safety because long-term steroid exposure can lead to serious side effects. The need for such therapies emphasizes the importance of innovative drug development and continued research into disease-modifying agents.

Looking to the future, participants identified several challenges that must be addressed to advance care further. Improving clinical trial design to better evaluate treatment outcomes and achieving consensus with regulatory agencies on metrics for success will be crucial for moving promising therapies forward. In addition, further characterization of disease pathogenesis, with a focus on individualized genetic and molecular profiles, is essential to enable more personalized, effective treatment plans for patients.

The meeting concluded with a collective expression of gratitude to all organizers and participants and a commitment to ongoing collaboration. Regular meetings such as this one will be vital for sustaining progress and fostering the innovations needed to transform patient care in pemphigus and pemphigoid.

KEYWORDS

International Pemphigus and Pemphigoid Foundation; Meeting report; Pemphigoid; Pemphigus; Thessaloniki

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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Conceptualization: APat, MK; Writing - Original Draft Preparation: MK; Writing - Review and Editing: MK, PD, DFM, APay, ES, VW, MY, JY, VA, LB, FC, DC, MD, DD, JF, CH, MHe, MHo, PJ, HK, EM, AM, MP, CP, MAS, AAS, FS, ES, KT, TJT, NVB, FV, SY, APat

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) OR LARGE LANGUAGE MODELS (LLMS)

The authors did not use AI/LLM in any part of the research process and/or manuscript

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