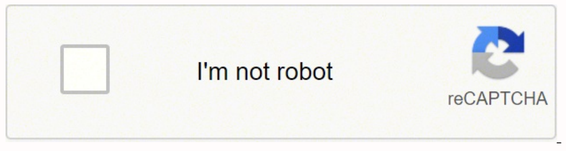

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2019, 80, 402–410. The “outside-in” hypothesis posits that physical changes in the epidermal structure (e.g., keratinocytes, proteins, lipids, pH) drive immune dysregulation, whereas the “inside-out” hypothesis suggests that aberrant immune activity (e.g., leukocytes, lymphocytes, cytokines, antimicrobial peptides) alters the skin-barrier [35]. Though eosinophils and mast cells can both be elevated in the skin and blood of AD patients, they likely play a lesser role in the pathogenesis of AD [84].The adaptive immune system is composed of antigen-specific lymphocytes (T-cells, B-cells) that utilize long-lasting, specific memory to direct the host immune response. Other topical PDE-4 inhibitors are currently in phase I, II, and II development [98]. 2000, 67, 1020–1024. 2004, 199, 125–130. Previously, AD was thought to be a disease of Th1/Th2 imbalance; however, more recent data suggest a biphasic T-cell response with additional roles played by Th17 and Th22 cells [85]. Systemic immunosuppressants, including cyclosporine A, methotrexate, azathioprine, and to a lesser extent, mycophenolate mofetil, demonstrated efficacy for moderate to severe AD in a variety of RCTs [95]. But “atopic” means that it affects parts of your skin that haven’t come in direct contact with the things you’re allergic or sensitive to. 1998, 39, 590–596. The FDA recently expanded dupilumab’s indication in 2019 for use in children ≥12 years old with AD, and investigation for use in infants and children with AD is currently ongoing. Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. [Google Scholar] [CrossRef] [PubMed]Kim, J.P.; Chao, L.X.; Simpson, E.L.; Silverberg, J.I. Persistence of atopic dermatitis (AD): A systematic review and meta-analysis. You may have flares, or times when your symptoms suddenly get worse, followed by stretches of time without symptoms. General support for this model is provided by the fact that many patients with AD have genetic polymorphisms in cytokines, chemokines, and receptors (including IL-4, IL-13, IL-18, IL-22, IL-31, CCL5, and CD14) [71,72,73,74], and treatment of human epidermal keratinocytes with many of these same mediators recapitulates the atopic dermatitis phenotype [75].The innate immune system is composed of soluble and cellular effectors that utilize germline-encoded pattern recognition receptors (PRRs). 2018, 32, 403–410. 2010, 24, 415–419. Tight junction-based epithelial microenvironment and cell proliferation. Cochrane Database Syst. [Google Scholar] [CrossRef]Gottlieb, A.B.; Blauvelt, A.; Thaçi, D.; Leonardi, C.L.; Poulin, Y.; Drew, J.; Peterson, L.; Arendt, C.; Burge, D.; Reich, K. 2008, 4, e1000038. Narrow band UVB: Is it effective and safe for paediatric psoriasis and atopic dermatitis? Immunity 2015, 42, 756–766. 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Emerging insights into relevant pathways, including recognition of the role of T-helper type 2 driven inflammation in AD and T-helper 1 and 17 driven inflammation in psoriasis, have led to a therapeutic revolution. Dandruff is just another name for mild seborrheic eczema on the scalp. Nearly one-half of childhood cases of psoriasis may first present in this way. Cell Biol. [Google Scholar] [CrossRef]Johnston, A.; Xing, X.; Wolterink, L.; Barnes, D.H.; Yin, Z.; Reingold, L.; Kahlenberg, J.M.; Harms, P.W.; Gudjonsson, J.E. IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. 58), 17–19. 2015, 173, 949–961. Venereol. Th1 and Th17 pathways in psoriasis) [18,19]. 2016, 375, 2335–2348. For psoriasis, Tazarotene is rarely used in children given the associated skin irritation, while anthralin and coal tar are limited by practical features associated with application: staining of skin and clothing (both agents) and malodor (coal tar).For the treatment of moderate-to-severe AD or psoriasis in children, treatment options include systemic therapy (most of which are used off-label), phototherapy, and biologic agents. Th17 cells, and to a lesser extent Th1 cells, are crucial for orchestrating the chronic, maintenance phase of psoriasis, and, as such, the p40 subunit presents a more specific target for psoriasis compared to TNF-α. A phase I double-blind, placebo controlled RCT showed that a single dose of nemolizumab in AD patients resulted in significant improvement in visual analog scale (VAS)-itch, sleep and decreased use of TCS compared to placebo [107]. Gene for familial psoriasis susceptibility mapped to the distal end of human chromosome 17q. Doctors recommend using these creams at night because they can leave residue on clothing. Both diseases result in chronic, systemic inflammation with increased circulating populations of leukocytes, lymphocytes, cytokines, and chemokines (predominantly Th2 pathways in AD vs. [Google Scholar] [CrossRef]Greb, J.E.; Goldminz, A.M.; Elder, J.T.; Lebwohl, M.G.; Gladman, D.D.; Wu, J.J.; Mehta, N.N.; Finlay, A.Y.; Gottlieb, A.B. Psoriasis. Cytokine 2015, 73, 311–318. [Google Scholar] [CrossRef]Samarasekera, E.J.; Sawyer, L.; Wonderling, D.; Tucker, R.; Smith, C.H. Topical therapies for the treatment of plaque psoriasis: Systematic review and network meta-analyses. 2019, 80, 390–401. 2011, 3, 180–186. 2014, 95, 162–172. What Are the Symptoms of Atopic Dermatitis? 2011, 41, 298–310. The processing of profilaggrin to filaggrin produces polycarboxylic acids (e.g., urocanic acid, pyrrolidone-5-carboxylic acid) known as natural moisturizing factors (NMFs) These NMFs promote hydration of the skin. Upadacitinib effect on pruritus in moderate-to-severe atopic dermatitis; from a phase 2b randomized, placebo-controlled trial. 2006, 126, 1396–1402. Recent studies focused extensively on the role Th17 cells in the pathogenesis of psoriasis, in part due to their high concentration in psoriatic lesions and significant reduction following anti-TNF-α treatment [126]. [Google Scholar] [CrossRef]Lebwohl, M.G.; Breneman, D.L.; Goffe, B.S.; Grossman, J.R.; Ling, M.R.; Milbauer, J.; Pincus, S.H.; Sibbald, R.G.; Swinyer, L.J.; Weinstein, G.D.; et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn’s disease: Unexpected results of a randomised, double-blind placebo-controlled trial. Br. J. [Google Scholar] [CrossRef]Engebretsen, K.A.; Johansen, J.D.; Kezic, S.; Linneberg, A.; Thyssen, J.P. The effect of environmental humidity and temperature on skin barrier function and dermatitis. 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Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): Results from two phase 3 randomised trials. Additional long-term studies are underway to better understand the efficacy and safety profile of JAK inhibitors.Psoriasis is estimated to affect 2–3% of the global population, corresponding to >125 million individuals [114,115]. [Google Scholar] [CrossRef]Jang, H.; Matsuda, A.; Jung, K.; Karasawa, K.; Matsuda, K.; Oida, K.; Ishizaka, S.; Ahn, G.; Amagai, Y.; Moon, C.; et al. [Google Scholar] [CrossRef]Ahmad-Nejad, P.; Mrabet-Dahbi, S.; Breuer, K.; Klotz, M.; Werfel, T.; Herz, U.; Heeg, K.; Neumaier, M.; Renz, H. Interestingly, even after discontinuation of treatment with secukinumab, approximately 20% maintained their response even after one year, suggesting the possibility of altering homeostatic set points with biologic therapy. 2017, 377, 1537–1550. However, given its more general role in the immune response, TNF-α inhibitors have a broad AE profile, especially with regard to increased infectious risk (e.g., conversation of tuberculosis from latent to active, reactivation of hepatitis B virus). Long-term safety experience of ustekinumab in patients with moderate to severe psoriasis (Part II of II): Results from analyses of infections and malignancy from pooled phase II and III clinical trials. Two phase III, double-blind, placebo controlled RCTs in adults and children showed that crisaborole was significantly more effective than vehicle with no major AEs other than application site reactions (e.g., stinging) [97]. New pathogenic and therapeutic paradigms in atopic dermatitis. Most people with atopic dermatitis use thick creams (called ointments or emollients) to keep their skin moisturized and their symptoms under control. 2018, 33, 173–180. The most common treatment-related AEs observed in both adolescents and adults included injection site reactions, conjunctivitis, and nasopharyngitis. Anti-Interleukin-31 Receptor A Antibody for Atopic Dermatitis. [Google Scholar] [CrossRef]Lebwohl, M.; Siskin, S.B.; Epinette, W.; Breneman, D.; Funicella, T.; Kalb, R.; Moore, J. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: A multicenter experience from Egypt. 2011, 365, 620–628. 2016, 375, 345–356. 2014, 134, 160–169. The role of air pollutants in atopic dermatitis. [Google Scholar] [CrossRef]Johnson-Huang, L.M.; McNutt, N.S.; Krueger, J.G.; Lowes, M.A. Cytokine-producing dendritic cells in the pathogenesis of inflammatory skin diseases. IL-23 inhibitors were well-tolerated and safe, with most AEs related to infection (upper respiratory infection, gastroenteritis, herpes simplex virus, tinea).Many of the Th17 and Th1 cytokines involved in the pathogenesis of psoriasis signal through JAK. 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Resource Links: MORE FROM SYMPTOMFIND.COM [Skip to Navigation] Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA Department of Dermatology, George Washington University School of Medicine, Washington, DC 20037, USA Author to whom correspondence should be addressed. Allergy 2014, 69, 28–36. They are less commonly used as first-line therapy owing to high cost, activity comparable to low potency TCS [92], slower onset than TCS, application site reactions (e.g., stinging, burning) and an FDA-issued black box warning for potential malignancy. Filaggrin breakdown products determine corneocyte conformation in patients with atopic dermatitis. 2011, 89, 432–437. Certolizumab pegol for the treatment of chronic plaque psoriasis: Results through 48 weeks from 2 phase 3, multicenter, randomized, double-blinded, placebo-controlled studies (CIMPASI-1 and CIMPASI-2). 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A phase II double-blind, placebo controlled RCT with upadacitinib (an oral JAK 1 inhibitor) monotherapy showed a significant decrease in EASI and NRS itch scores at 16 weeks (primary endpoint) and 32 weeks (long-term extension) [113]. Once the gold standard for targeted phototherapy, PUVA has fallen out of favor due to its carcinogenic effects and association with squamous cell carcinoma and melanoma of the skin [178,179].As was previously discussed for AD, systemic immunosuppressants, including methotrexate (the first systemic therapy approved for psoriasis) and cyclosporine A, have shown efficacy in treating moderate-to-severe psoriasis, but are limited by their relative non-specificity and broad AE profile. Pediatrics 2013, 172, 351–356. 2006, 55, 598–606. [Google Scholar] [CrossRef]Tomfohrde, J.; Silverman, A.; Barnes, R.; Fernandez-Vina, M.A.; Young, M.; Lory, D.; Morris, L.; Wuepper, K.D.; Stastny, P.; Menter, A. 2016, 75, 297–305. 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Psoriasis is an immune-mediated disease characterized by cycles of sustained inflammation and remission, uncontrolled keratinocyte proliferation, and impaired keratinocyte differentiation. Currently, the only FDA-approved biologics in children are etanercept (≥4 years old) and ustekinumab (≥12 years old), with ongoing studies for many of the newer treatment classes. [Google Scholar] [CrossRef] [PubMed]Patel, K.R.; Immaneni, S.; Singam, V.; Rastogi, S.; Silverberg, J.I. Association between atopic dermatitis, depression, and suicidal ideation: A systematic review and meta-analysis. Pract. Th17 cells are a subset of T-lymphocytes that specialize in epithelial surveillance and defense against extracellular pathogens through production of IL-17, IL-23, and IL-22. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: Results from two randomized, placebo-controlled, phase III trials. 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In phase II and III double-blind, placebo controlled RCTs, patients with moderate to severe AD treated with dupilumab showed significant improvement in a number of primary and secondary outcomes including clinician reported outcomes (e.g., Eczema Area and Severity Index (EASI), SCORing Atopic Dermatitis (SCORAD), body surface area (BSA) involvement, investigators global assessment (IGA)) and patient-reported outcomes (e.g., pruritus numeric rating scale (NRS), Patient-Oriented Eczema Measure (POEM), and Dermatology Life Quality Index (DLQI)) [100,101,102,103]. 2018, 6, 1306–1312. 2012, 90, 784–795. 2005, 202, 135–143. In recent years, a better understanding of the underlying pathologic mechanisms in both conditions has led to a revolution in the development of novel, targeted therapies.This manuscript reviews the pathophysiology of AD and psoriasis, current and novel therapeutics, and implications for management in children.Atopic dermatitis affects up to 15–20% of children and 1–10% of adults worldwide [20]. These cells also secrete a number of pro-inflammatory cytokines, such as TNF-α, IL-12, and IL-23, resulting in the differentiation and activation of activation of Th1, Th17, and Th22 cells.Without specific therapeutic intervention, activation of adaptive immunity drives the self-sustaining, maintenance phase of inflammation in psoriasis [124]. [Google Scholar] [CrossRef] [PubMed]Cheng, B.T.; Silverberg, J.I. Depression and psychological distress in US adults with atopic dermatitis. Keratinocytes, which also function as a physical barrier and sensory cell in the innate immunity, produce pro-inflammatory cytokines in response to AMP-nucleic acid complexes, including type I IFNs, TNF-α, IL-1, and IL-6 [122]. 2019, 81. Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. 2006, 78, 827–851. 2004, 51, 704–708. Type 2 innate lymphoid cells (ILCs) also show increased activity in AD patients and contribute to DC activation by producing IL-5 and IL-13 [83]. 2019, 139, 1480–1489. Keratinocyte-derived IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) are increased in atopic skin and contribute to activation of DCs, type 2 ILCs, and type 2 inflammation. Gut 2012, 61, 1693–1700. Crisaborole was recently added as an additional first-line topical option in AD, and the combination of its relatively specific mode of action, non-steroidal formulation, and promising long-term safety data make it an important addition to the pediatric AD arsenal [225]. 2017, 31, 507–517. Proc. Evidence for a streptococcal superantigen-driven process in acute guttate psoriasis. [Google Scholar] [CrossRef]McKenzie, C.; Silverberg, J.I. The prevalence and persistence of atopic dermatitis in urban United States children. 2009, 129, 1892–1908. 2016, 174, 296–304. [Google Scholar] [CrossRef] [PubMed]Kreuter, A.; Sommer, A.; Hyun, J.; Bräutigam, M.; Brockmeyer, N.H.; Altmeyer, P.; Gambichler, T. Association between atopic dermatitis and obesity in adulthood. 1994, 94, 202–209. 2016, 175, 357–363. Science 1994, 264, 1141–1145. 2015, 172, 320–321. Skin Res. Mol. Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. 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Previous studies found that lesional skin from AD patients had significant barrier dysfunction compared to healthy controls. [Google Scholar] [CrossRef] [PubMed]Liu, F.-T.; Goodarzi, H.; Chen, H.-Y. Common triggers include fragrances, laundry detergents and soaps. Targeted treatments have filled many unmet needs for both of these conditions. New insights of T cells in the pathogenesis of psoriasis. [Google Scholar] [CrossRef] [PubMed]McGill, A.; Frank, A.; Emmett, N.; Turnbull, D.M.; Birch-Machin, M.A.; Reynolds, N.J. The anti-psoriatic drug anthralin accumulates in keratinocyte mitochondria, dissipates mitochondrial membrane potential, and induces apoptosis through a pathway dependent on respiratory competent mitochondria. Symptoms of atopic dermatitis tend to come and go. Lancet 2017, 390, 276–288. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: A systematic review. Lancet 2008, 371, 1665–1674. 2008, 358, 241–251. 2008, 27, 144–150. Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): A randomised, double-blind, active-comparator-controlled phase 3 trial. Lancet 2019. In multiple phase III double-blind, placebo controlled RCTs, patients with moderate-to-severe plaque or palmoplantar psoriasis treated with apremilast showed significant improvement in PASI-50 (Psoriasis Area and Severity Index, ≥50% reduction from baseline), PASI-75, and static investigators global assessment (sIGA) at week 16 [183,184,185,186]. [Google Scholar] [CrossRef] [PubMed]Morizane, S.; Yamasaki, K.; Mühleisen, B.; Kotol, P.F.; Murakami, M.; Aoyama, Y.; Iwatsuki, K.; Hata, T.; Gallo, R.L. Cathelicidin antimicrobial peptide LL-37 in psoriasis enables keratinocyte reactivity against TLR9 ligands. 2017, 377, 1525–1536. Acitretin is an oral second-generation retinoid that is approved for the treatment of moderate-to-severe psoriasis and is particularly efficacious for pustular psoriasis, erythrodermic psoriasis, and as an adjunct to phototherapy [180]. [Google Scholar] [CrossRef] [PubMed]Totri, C.R.; Eichenfield, L.F.; Logan, K.; Proudfoot, L.; Schmitt, J.; Lara-Corrales, I.; Sugarman, J.; Tom, W.; Siegfried, E.; Cordoro, K.; et al. [Google Scholar] [CrossRef] [PubMed]Roekevisch, E.; Spuls, P.I.; Kuester, D.; Limpens, J.; Schmitt, J. [Google Scholar] [CrossRef]Rebane, A.; Zimmermann, M.; Aab, A.; Baurecht, H.; Koreck, A.; Karelson, M.; Abram, K.; Metsalu, T.; Pihlap, M.; Meyer, N.; et al. [Google Scholar] [CrossRef]Niebuhr, M.; Langnickel, J.; Draing, C.; Renz, H.; Kapp, A.; Werfel, T. Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. Photo Courtesy: Igor Alecsander/E+/Getty Images Dermatitis is a broad term that means any inflammation or irritation of the skin — so most itchy, red rashes can be called dermatitis. Treatment of plaque psoriasis with an ointment formulation of the Janus kinase inhibitor, tofacitinib: A Phase 2b randomized clinical trial. [Google Scholar] [CrossRef]Kelly-Welch, A.E.; Hanson, E.M.; Boothby, M.R.; Keegan, A.D. Interleukin-4 and interleukin-13 signaling connections maps. Both AD and psoriasis are caused by a complex combination of immune dysregulation, skin-barrier disruption, genetic factors, and environmental influences. [Google Scholar] [CrossRef] [PubMed]Simpson, E.L.; Flohr, C.; Eichenfield, L.F.; Bieber, T.; Sofen, H.; Taïeb, A.; Owen, R.; Putnam, W.; Castro, M.; DeBusk, K.; et al. 2019, 33, 1341–1348. 2018, 178, 114–123. [Google Scholar] [CrossRef]Levy, L.L.; Urban, J.; King, B.A. Treatment of recalcitrant atopic dermatitis with the oral Janus kinase inhibitor tofacitinib citrate. FASEB J. IgE, mast cells, and eosinophils in atopic dermatitis. 2012, 129, 1297–1306. Kantor and Silverberg have recently reviewed the topic of environmental risk factors in AD [69].Thus, a variety of factors contribute to dysfunction of the physical epidermal barrier, resulting in keratinocyte damage, enhanced antigen and allergen penetration, and increased microbial signaling, ultimately resulting in immune cell activation, cytokine production, and inflammation.According to the inside-out hypothesis of AD, dysregulation of the immune system results in disruption of the keratinocyte barrier and inflammation [70]. [Google Scholar] [CrossRef]Trembath, R.C.; Clough, R.L.; Rosbotham, J.L.; Jones, A.B.; Camp, R.D.; Frodsham, A.; Browne, J.; Barber, R.; Terwilliger, J.; Lathrop, G.M.; et al. 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Inside out or outside in: Does atopic dermatitis disrupt barrier function or does disruption of barrier function trigger atopic dermatitis? Here, we review the complex pathophysiology of both AD and psoriasis and discuss the implications for treatment with current state-of-the-art and emerging topical and systemic therapies. Though apremilast does not carry the same immunosuppression risks as biologic therapy, it is overall less efficacious with only approximately 30% of patients achieving PASI-75 scores at week 16.TNF-α inhibitors are the first generation of biologic medications for psoriasis, and they have been successfully used to treat moderate-to-severe psoriasis for over a decade. Fine mapping of the psoriasis susceptibility locus PSORS1 supports HLA-C as the susceptibility gene in the Han Chinese population. Topical corticosteroids in plaque psoriasis: A systematic review of efficacy and treatment modalities. 2017, 76, 60–69.e69. [Google Scholar] [CrossRef] [PubMed]Gfatter, R.; Hackl, P.; Braun, F. Toward a major risk factor for atopic eczema: Meta-analysis of filaggrin polymorphism data. 1974, 109, 207–211. Tazarotene was the first retinoid developed for treatment of psoriasis, and, while efficacious, its continuous use is limited by local irritation. [Google Scholar] [CrossRef]Bowcock, A.M.; Krueger, J.G. Getting under the skin: The immunogenetics of psoriasis. [Google Scholar] [CrossRef] [PubMed]Chiesa Fuxench, Z.C.; Block, J.K.; Boguniewicz, M.; Boyle, J.; Fonacier, L.; Gelfand, J.M.; Grayson, M.H.; Margolis, D.J.; Mitchell, L.; Silverberg, J.I.; et al. 2014, 94, 640–644. 2012, 26 (Suppl. A review of acitretin, a systemic retinoid for the treatment of psoriasis. Jonathan I. [Google Scholar] [CrossRef]Silverberg, J.I.; Gelfand, J.M.; Margolis, D.J.; Boguniewicz, M.; Fonacier, L.; Grayson, M.H.; Ong, P.Y.; Chiesa Fuxench, Z.C.; Simpson, E.L. Symptoms and diagnosis of anxiety and depression in atopic dermatitis in U.S. adults. [Google Scholar] [CrossRef]Gittler, J.K.; Shemer, A.; Suárez-Fariñas, M.; Fuentes-Duculan, J.; Gulewicz, K.J.; Wang, C.Q.F.; Mitsui, H.; Cardinale, I.; de Guzman Strong, C.; Krueger, J.G.; et al. As such, TCIs are still recommended for topical treatment of AD in infants, children and adults [91].Systemic corticosteroids, unlike TCS, universally suppress immune activity. Photo Courtesy: hiraman/E+/Getty Images Some people use the terms “atopic dermatitis” and “eczema” to mean the same thing, while others describe atopic dermatitis as a type of eczema. Previous treatments for both diseases were limited to anti-inflammatory agents that broadly suppress inflammation. 2004, 9, 140–147. Signaling by IL-31 and functional consequences. Psoriasis. 2007, 122, 201–206. [Google Scholar] [CrossRef] [PubMed]Silverberg, J.I.; Garg, N.K.; Paller, A.S.; Fishbein, A.B.; Zee, P.C. 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Representing the next generation of biologic therapy after TNF-α inhibitors, ustekinumab is a fully human IgG1 monoclonal antibody against the shared p40 subunit of IL-12 and IL-23, thus blocking two distinct pathways of T-cell activity: Th1 and Th17, respectively [187]. However, variability in these loci are thought to only account for about 30% of heritability, suggesting a cumulative effect from multiple mutations with smaller individual effects and/or undetected gene-gene interactions. 2016, 75, 1119–1125.e1111. [Google Scholar] [CrossRef]Gudjonsson, J.E.; Elder, J.T. Psoriasis: Epidemiology. Topical vitamin D analogs (including calcitriol, calcipotriene, and tacalcitol) have broad effects of keratinocyte proliferation, apoptosis, and immunomodulation [167]. Expert Rev. Primary or secondary endpoints for the phase III double-blind, placebo controlled RCTs of the IL-23 inhibitors were measured with PASI-90 (guselkumab: week 16, 70–85%; tildrakizumab: week 12, 35%; risankizumab: week 16, 72–75%) and PASI-100 scores, representing a remarkable improvement in treatment specificity [211,212,213,214,215,216]. Raj Chovatiya is supported by a grant from the National Institutes of Health T32AR060710. In contrast, an alternative to UVB-based therapy is psoralen combined with UVA (PUVA). Both words refer to a common skin condition that causes a red, itchy rash. [Google Scholar] [CrossRef] [PubMed]Zaba, L.C.; Cardinale, I.; Gilleaudeau, P.; Sullivan-Whalen, M.; Suárez-Fariñas, M.; Fuentes-Duculan, J.; Novitskaya, I.; Khatcherian, A.; Bluth, M.J.; Lowes, M.A.; et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). 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Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: Long-term efficacy and safety results from 2 randomized phase-III studies and 1 open-label long-term extension study. Methotrexate treatment in 13 children with severe plaque psoriasis. [Google Scholar] [CrossRef]Czarnowicki, T.; Malajian, D.; Khattri, S.; Correa da Rosa, J.; Dutt, R.; Finney, R.; Dhingra, N.; Xiangyu, P.; Xu, H.; Estrada, Y.D.; et al. Though still used today, these therapies have largely been replaced by TCS. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: A phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. [Google Scholar] [CrossRef] [PubMed]Szegedi, A. The outermost skin-barrier is composed of the cornified envelope, a highly cross-linked, flexible, insoluble structure composed of corneocytes, lipids, involucrin, loricrin, and filaggrin. 2018, 19, S77–S78. Apremilast, an oral PDE-4 inhibitor that is approved for the treatment of moderate-to-severe psoriasis, has also been studied in AD. During a flare of atopic dermatitis, your doctor may prescribe a steroid cream to help control your immune system and reduce inflammation. Studies of HLA-Cw6 showed several important associations: overall increased risk of psoriasis, especially in white and Chinese populations [141,142]; early-onset and more severe disease, especially in those with positive family history [141,143]; guttate psoriasis and streptococcal pharyngitis, but not pustular psoriasis [143,144]. 2019. 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A proteolytic cascade of kallikreins in the stratum corneum. 2007, 204, 3183–3194. 2005, 5, 699–711. 2005, 124, 103–106. 2016, 75, 494–503.e496. The latest generation of biologic medications approved by the FDA for use in moderate-to-severe psoriasis are the IL-23 inhibitors: guselkumab in 2017; tildrakizumab in 2018; and risankizumab in 2019, all of which are human monoclonal IgG1 antibodies against the p19 subunit of IL-23 [187]. Allergy Asthma Immunol. Symp. Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: Results of the randomized phase 3 CADMUS study. [Google Scholar] [CrossRef]Ludwig, R.J.; Herzog, C.; Rostock, A.; Ochsendorf, F.R.; Zollner, T.M.; Thaci, D.; Kaufmann, R.; Vogl, T.J.; Boehncke, W.-H. [Google Scholar] [CrossRef]Nograles, K.E.; Davidovici, B.; Krueger, J.G. New insights in the immunologic basis of psoriasis. A recent phase II showed no difference compared to vehicle at lower doses and modest (but statistically significant) improvement in AD at higher doses [99]. [Google Scholar] [CrossRef]Cai, Y.; Fleming, C.; Yan, J. [Google Scholar] [CrossRef] [PubMed]Farber, E.M.; Nall, M.L.; Watson, W. [Google Scholar] [CrossRef]Asumalahti, K.; Laitinen, T.; Itkonen-Vatjus, R.; Lokki, M.L.; Suomela, S.; Snellman, E.; Saarialho-Kere, U.; Kere, J. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: A randomised, placebo-controlled, dose-ranging phase 2b trial. Adalimumab showed higher efficacy in head-to-head comparison with methotrexate. A number of other topical and/or oral JAK inhibitors are currently under investigation for treatment of AD. A decrease in NMFs as a result of impaired profilaggrin cleavage decreases osmotic draw and results in increased TEWL [44].NMFs and other acidic metabolites, including free fatty acids, function more broadly in decreasing skin surface pH [45]. 2017, 77, 641–649.e645. 2015, 6, 7001. [Google Scholar] [CrossRef] [PubMed]Nestle, F.O.; Turka, L.A.; Nickoloff, B.J. Characterization of dermal dendritic cells in psoriasis. 1997, 6, 813–820. [Google Scholar] [CrossRef]Kobayashi, T.; Glatz, M.; Horiuchi, K.; Kawasaki, H.; Akiyama, H.; Kaplan, D.H.; Kong, H.H.; Amagai, M.; Nagao, K. PDE-4 is responsible for degrading cAMP in immune cells, which promotes the expression of pro-inflammatory cytokines like IFN-γ and IL-17 and inhibits production of anti-inflammatory cytokines such as IL-10 [96]. They are often used as monotherapy in mild to moderate disease and in combination with systemic, biologic, or phototherapy in moderate to severe cases. PLoS ONE 2016, 11, e0161759. Apremilast for the treatment of moderate-to-severe palmoplantar psoriasis: Results from a double-blind, placebo-controlled, randomized study. IL-1, IL-8, and IL-36 appear to be important for neutrophilic activity in pustular psoriasis [129,130], whereas guttate psoriasis may be driven by streptococcal superantigen mediated activation of TCRs and subsequent molecular mimicry of keratin proteins [131,132].Early epidemiologic studies suggested a genetic component to psoriasis, as patients with psoriasis had higher incidence of disease among first and second-degree relatives compared to the general population, and monozygotic twins had two to threefold higher risk of psoriasis compared to dizygotic twins [133,134,135]. [Google Scholar] [CrossRef]Papp, K.A.; Langley, R.G.; Lebwohl, M.; Krueger, G.G.; Szapary, P.; Yeilding, N.; Guzzo, C.; Hsu, M.-C.; Wang, Y.; Li, S.; et al. Pompholyx eczema: This type of eczema causes painful blisters and scaly patches of skin that flake or crack. Nat. [Google Scholar] [CrossRef]Blauvelt, A.; Reich, K.; Tsai, T.-F.; Tyring, S.; Vanaclocha, F.; Kingo, K.; Ziv, M.; Pinter, A.; Vender, R.; Hugot, S.; et al. 2014, 170, 617–624. 2017, 76, 418–431. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. Lancet 1999, 353, 1589–1590. What’s the Difference Between Atopic Dermatitis and Other Types of Eczema? Lebrikizumab in combination with TCS showed promising results in a phase II study with significant improvement in the proportion of patients achieving ≥50% reduction in EASI from baseline (EASI-50) at 12 weeks compared to placebo [105]. 2000, 9, 1533–1542. Common AEs associated with TNF-α and IL-12/IL-23 inhibitors use in children include injection site reactions, nasopharyngitis, mild upper respiratory infection (similar to those normally seen in children), and headache.Improved understanding of the pathophysiology of AD and psoriasis has led to a revolution in targeted therapy. Filaggrin, cleaved from its precursor profilaggrin, plays a key role in aligning and securing corneocytes, protein fibrils, and lamellar sheets [40]. [Google Scholar] [CrossRef]Hueber, W.; Sands, B.E.; Lewitzky, S.; Vandemeulebroecke, M.; Reinisch, W.; Higgins, P.D.R.; Wehkamp, J.; Feagan, B.G.; Yao, M.D.; Karczewski, M.; et al. Overall, while IL-17 inhibitors were well-tolerated and safe, AEs included upper respiratory infections, nasopharyngitis, and candidal infections, underscoring the important role of Th17 cells in extracellular defense at epithelial surfaces. 2015, 135, 56–66. [Google Scholar]Paller, A.S.; Tom, W.L.; Lebwohl, M.G.; Blumenthal, R.L.; Boguniewicz, M.; Call, R.S.; Eichenfield, L.F.; Forsha, D.W.; Rees, W.C.; Simpson, E.L.; et al. [Google Scholar] [CrossRef]Marrakchi, S.; Guigue, P.; Renshaw, B.R.; Puel, A.; Pei, X.-Y.; Fraitag, S.; Zribi, J.; Bal, E.; Cluzeau, C.; Chrabieh, M.; et al. Dupilumab demonstrated an excellent safety profile with mainly mild or moderate AEs, including injection site reactions and ocular AEs (dry eye, eye pruritus, blepharitis, conjunctivitis, keratitis), with no increases of infection or malignancy overall, and lower rates of bacterial skin infection compared to placebo.There are currently ongoing studies examining the impact of monoclonal antibodies targeting IL-13 (lebrikizumab and tralokinumab), which are even more specific than targeting IL4 and IL13 for AD [104]. Cyclosporin in the treatment of patients with atopic eczema—A systematic review and meta-analysis. Despite the incongruity in the sequence of events, both models agree upon many of the same common mechanisms that result in chronic inflammation.The physical barrier function of the epidermis is crucial for protection against pathogens, allergens, toxins, and other irritants and maintenance of appropriate skin hydration. Their role in pathogenesis still remains unclear. A randomized phase 2a efficacy and safety trial of the topical Janus kinase inhibitor tofacitinib in the treatment of chronic plaque psoriasis. methotrexate vs. 2006, 142, 1138–1143. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. 2013, 133, 377–385. Allergy 2015, 70, 1300–1308. 2014, 133, 429–438. PSORS1 is located in the major histocompatibility complex (MHC) on chromosome 6p21, spanning a 220 kb segment class I telomeric region of human leukocyte antigen B (HLA-B). Tralokinumab in combination with mid-potency TCS was effective in a phase II RCT in adults and showed significant improvement in EASI, DLQI, SCORAD, and NRS-itch scores with a significant proportion of patients achieving EASI-50 and EASI-75 at 12 weeks compared to placebo [106].Nemolizumab, a humanized monoclonal antibody targeting the IL-31 receptor (a major signaling pathway for itch in AD), is currently in development. [Google Scholar] [CrossRef]Veal, C.D.; Clough, R.L.; Barber, R.C.; Mason, S.; Tillman, D.; Ferry, B.; Jones, A.B.; Ameen, M.; Balendran, N.; Powis, S.H.; et al. A phase II double-blind, placebo controlled RCT with baricitinib (an oral selective JAK 1 and 2 inhibitor) in combination with TCS showed improvement in inflammation and pruritus with significantly more patients achieving EASI-50 at 16 weeks compared to placebo [112]. Dupilumab shows long-term safety and efficacy in moderate-to-severe atopic dermatitis patients enrolled in a phase 3 open-label extension study. [Google Scholar] [CrossRef] [PubMed]Lebwohl, M.; Strober, B.; Menter, A.; Gordon, K.; Weglowska, J.; Puig, L.; Papp, K.; Spelman, L.; Toth, D.; Kerdel, F.; et al. While TCS are overall safe, efficacious, and well tolerated for a wide spectrum of disease, adverse effects (AEs) of their chronic use include skin atrophy, fragility, striae, poor wound healing, local immunosuppression, and potential systemic absorption leading to adrenal insufficiency. Common side effects of chronic systemic corticosteroid use in children are similar to those in adults and include immune suppression, hyperglycemia, weight gain, insomnia, gastroesophageal reflux, osteonecrosis, and adrenal insufficiency.For both AD and psoriasis, phototherapy with either NB-UVB or excimer laser can be preferable to systemic immunosuppressive therapy in children given the limited AEs. Uncontrolled studies support its efficacy; however, multiple sessions per week in-office can be challenging for children and caregivers, and there continues to be concern about long-term exposure to UVB light starting in childhood [234,235,236].Dupilumab is currently the only biologic agent available for the treatment of AD, though many new biologics are under investigation. [Google Scholar] [CrossRef] [PubMed]Wollenberg, A.; Howell, M.D.; Guttman-Yassky, E.; Silverberg, J.I.; Kell, C.; Ranade, K.; Moate, R.; van der Merwe, R. [Google Scholar] [CrossRef]Hartwig, I.R.V.; Sly, P.D.; Schmidt, L.A.; van Lieshout, R.J.; Bienenstock, J.; Holt, P.G.; Arck, P.C. Prenatal adverse life events increase the risk for atopic diseases in children, which is enhanced in the absence of a maternal atopic predisposition. As discussed earlier, apremilast is a small molecule inhibitor of the PDE-4 enzyme that reduces the level of pro-inflammatory Th17 cytokines and increases expression of IL-10 [182]. 1994, 130, 1402–1407. While some clinical characteristics are more common in children (e.g., ventral wrist dermatitis), others are more common in adults (e.g., hand and foot dermatitis, nipple eczema, thinning of the eyebrows, modification of disease course by emotional or environmental factors) [24].AD is characterized by dysfunction in both non-immune and immune components of the skin-barrier. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: A phase III, randomized controlled trial (ESTEEM 2). Expert Opin. [Google Scholar] [CrossRef]Czarnowicki, T.; Krueger, J.G.; Guttman-Yassky, E. 2005, 115, 828–833. Moisturizers and emollients restore the dysfunctional epidermal barrier by reducing TEWL and in certain formulations, replacing and supplementing lipids [90]. [Google Scholar] [CrossRef] [PubMed]Fan, X.; Yang, S.; Huang, W.; Wang, Z.-M.; Sun, L.-D.; Liang, Y.-H.; Gao, M.; Ren, Y.-Q.; Zhang, K.-Y.; Du, W.-H.; et al. [Google Scholar] [CrossRef]McFadden, J.; Valdimarsson, H.; Fry, L. Effects of soap and detergents on skin surface pH, stratum corneum hydration and fat content in infants. 2008, 158, 558–566. [Google Scholar] [CrossRef]Fluhr, J.W.; Elias, P.M. Stratum corneum pH: Formation and Function of the ‘Acid Mantle’. Cutis 2015, 96, 359–361. 2002, 1, 163–175. 2014, 2, 371–379. [Google Scholar] [CrossRef] [PubMed]Oiso, N.; Fukai, K.; Ishii, M. IL-22-producing “T22” T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. What Are the Treatments for Atopic Dermatitis? Topical calcineurin inhibitors (TCIs), including tacrolimus and pimecrolimus, inhibit calcineurin signaling thereby inhibiting T-cell activation. Dermatitis 2016, 27, 50–58. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: Double-blind, randomized controlled trial and open-label extension study. Vitamin D analogs in the treatment of psoriasis: Where are we standing and where will we be going? [Google Scholar] [CrossRef] [PubMed]Cury Martins, J.; Martins, C.; Aoki, V.; Gois, A.F.T.; Ishii, H.A.; da Silva, E.M.K. Topical tacrolimus for atopic dermatitis. [Google Scholar] [CrossRef]Ong, P.Y.; Ohtake, T.; Brandt, C.; Strickland, I.; Boguniewicz, M.; Ganz, T.; Gallo, R.L.; Leung, D.Y.M. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: Double-blind placebo-controlled randomised phase III trial. Numerous GWAS studies identified variants in cytokines, receptors, and signaling pathways that are critical for Th17 cell function: IL-23R (the receptor that binds to IL-23 and promotes activation and expansion of Th17 cells); IL-12B (the shared p40 subunit of IL-23 and IL-12); STAT3 (a signal transducer in the JAK/STAT signaling pathway downstream of several cytokine receptors including IL-23R); and Runx1 (a transcription factor important in Th17 cell differentiation) [153,155,156,157,158]. Seborrheic eczema: This type of eczema affects oily parts of the skin like the scalp, chest and sides of the nose. 1991, 125, 443–447. Guidelines of care for the management of atopic dermatitis: Section 2. Derm. [Google Scholar] [CrossRef]Collin, B.; Vani, A.; Ogboli, M.; Moss, C. Acidic skin pH (4–6) is important for appropriate expression, confirmation, and modification of epidermal proteins [46], inhibition (e.g., proteases) and activation (e.g., lipases) of enzymes that are critical for barrier function [47,48], and regulation of nonpathogenic skin flora [49]. 2014, 71, 116–132. [Google Scholar] [CrossRef] [PubMed]Gelfand, J.M.; Feldman, S.R.; Stern, R.S.; Thomas, J.; Rolstad, T.; Margolis, D.J. Determinants of quality of life in patients with psoriasis: A study from the US population. Other psoriasis susceptibility loci include PSORS2 on chromosome 17q24–q25, which spans the gene for caspase recruitment domain-containing protein 14 (CARD14), a scaffolding protein involved triggering NF-κB activation [145,146]; PSORS4 on chromosome 1q which spans the epidermal differentiation complex [147]; PSORS6 on chromosome 19p13, which spans the gene for tyrosine kinase 2 (TYK2) [148]; PSORS7 on chromosome 1p, which spans the gene for IL-23 receptor (IL-23R) [149].Genome-wide association studies (GWAS) have largely confirmed the findings from previous linkage studies, including the importance of the PSORS1 and the MHC locus [150,151,152], while identifying additional risk loci through high resolution analyses of small nucleotide polymorphisms (SNPs) in large sample populations [153,154]. Acta Derm. 2018, 121, S21. Etanercept (a recombinant human fusion protein consisting of the TNF-α receptor protein and Fc portion of immunoglobulin IgG1) was first-in-class and approved by the FDA in 2004, followed by infliximab (a human-murine chimeric monoclonal IgG1 antibody against TNF-α) in 2006, adalimumab (the first fully human monoclonal IgG1 antibody against TNF-α) in 2008, and certolizumab (a recombinant humanized IgG1 antibody Fab fragment against TNF-α conjugated to polyethylene glycol) in 2018 [187]. Skin barrier and immune dysregulation in atopic dermatitis: An evolving story with important clinical implications. [Google Scholar] [CrossRef]Seidenari, S.; Giusti, G. Raj Chovatiya declares no competing interests.Silverberg, J.I.; Silverberg, N.B.; Lee-Wong, M. 2007, 80, 273–290. 2009, 41, 199–204. Ann. Topical corticosteroids (TCS) act broadly to suppress the activity of innate and adaptive immune cells. For children with psoriasis, etanercept [238], adalimumab [239], and ustekinumab [240] have been studied in phase III double-blind, placebo controlled RCTs. All three agents showed comparable efficacy and safety to the previous adult trials. As was seen with IL-17 inhibitors, about one-quarter of patients who discontinued therapy with risankizumab after 16 weeks maintained their response even after 48 weeks, again suggesting the possibility for long-term modification of cytokine signaling pathways with biologic therapy. BMC Dermatol. Efficacy of topical calcineurin inhibitors in psoriasis. [Google Scholar] [CrossRef]Reich, K.; Papp, K.A.; Blauvelt, A.; Tyring, S.K.; Sinclair, R.; Thaçi, D.; Nograles, K.; Mehta, A.; Cichanowitz, N.; Li, Q.; et al. A multicenter trial of calcipotriene ointment and halobetasol ointment compared with either agent alone for the treatment of psoriasis. 2017, 35, 283–289. 2012, 44, 1341–1348. While exact identification has been technically challenging due to strong linkage disequilibrium, most studies agree that HLA-Cw6 is the susceptibility allele in PSORS1 [141]. 2013, 24, 476–486. 1995, 75, 429–433. [Google Scholar] [CrossRef] [PubMed]Duvic, M.; Asano, A.T.; Hager, C.; Mays, S. 2010, 29, 3–9. [Google Scholar] [CrossRef]Hanifin, J.M.; Ellis, C.N.; Frieden, I.J.; Fölster-Holst, R.; Stein Gold, L.F.; Secci, A.; Smith, A.J.; Zhao, C.; Kornyeyeva, E.; Eichenfield, L.F. OPA-15406, a novel, topical, nonsteroidal, selective phosphodiesterase-4 (PDE4) inhibitor, in the treatment of adult and adolescent patients with mild to moderate atopic dermatitis (AD): A phase-II randomized, double-blind, placebo-controlled study. 2012, 132, 135–143. While infectious complications were the most serious AEs associated with ustekinumab, the overall rate of infections was lower than that seen with TNF-α inhibitors [201].Highlighting an evolving understanding of the immunological basis of psoriasis, the third generation of biologic medications approved by the FDA was the IL-17 inhibitors: secukinumab (a fully human monoclonal IgG1 antibody against IL-17A) in 2015; ixekizumab (a humanized monoclonal IgG4 antibody against IL-17A) in 2016; brodalumab (a human monoclonal IgG2 antibody against IL-17RA) in 2017 [187]. Abnormal epidermal barrier in the pathogenesis of atopic dermatitis. Other systemic therapies have limited data to support use, including mycophenolate mofetil and azathioprine. 2), 28–33. Psoriasis is associated with rheumatologic (psoriatic arthritis), cardiovascular, metabolic, hepatic, and psychiatric disease [8,9,10,11]. [Google Scholar] [CrossRef]Stern, R.S.; Study, P.F.-U. Systemic corticosteroids are generally contraindicated for management of AD and psoriasis despite continued inappropriate use especially in childhood AD [233], and they should only be used as bridge therapy, for immediate relief, or when other options are not available. Primers 2018, 4, 1–20. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: Results of the randomized, double-blind, phase III NAVIGATE trial. [Google Scholar] [CrossRef]Menter, A.; Feldman, S.R.; Weinstein, G.D.; Papp, K.; Evans, R.; Guzzo, C.; Li, S.; Dooley, L.T.; Arnold, C.; Gottlieb, A.B. A randomized comparison of continuous vs. Numerous randomized controlled trials (RCTs) demonstrated efficacy for both reactive and proactive treatment protocols [91]. 2016, 75, 506–515. The mechanism of phototherapy is believed to be multifactorial, including induction of apoptosis in keratinocytes, APCs, and Th17 cells, and promotion of regulatory T-cell (Treg) activation [176]. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. [Google Scholar] [CrossRef]Cornelissen, C.; Lüscher-Firzlaff, J.; Baron, J.M.; Lüscher, B. AEs include nausea, diarrhea, and weight loss, which can be quite significant and chronic in some patients. [Google Scholar] [CrossRef] [PubMed]Papp, K.A.; Menter, M.A.; Raman, M.; Disch, D.; Schlichting, D.E.; Gaich, C.; Macias, W.; Zhang, X.; Janes, J.M. A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with

moderate-to-severe psoriasis. N. [Google Scholar] [CrossRef] [PubMed]Langley, R.G.; Elewski, B.E.; Lebwohl, M.; Reich, K.; Griffiths, C.E.M.; Papp, K.; Puig, L.; Nakagawa, H.; Spelman, L.; Sigurgeirsson, B.; et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. In particular, LL37 complexes with self-genetic material and binds to TLR7, TLR8, and TLR9, resulting in the secretion of type I interferons (IFN-α and IFN-β) and a break in immunologic tolerance [119,120,121]. [Google Scholar] [CrossRef] [PubMed]Simpson, E.L.; Bieber, T.; Guttman-Yassky, E.; Beck, L.A.; Blauvelt, A.; Cork, M.J.; Silverberg, J.I.; Deleuran, M.; Kataoka, Y.; Lacour, J.-P.; et al. 2017, 119, 548–552.e543. Clin. [Google Scholar] [CrossRef]Eberlein-König, B.; Schäfer, T.; Huss-Marp, J.; Darsow, U.; Möhrenschlager, M.; Herbert, O.; Abeck, D.; Krämer, U.; Behrendt, H.; Ring, J. Immunol. Natural history of psoriasis in 61 twin pairs. 2017, 139, S65–S76. 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Tight junction defects in patients with atopic dermatitis. 2009, 129, 320–322. Genes Immun. Th17 cells, a subset of T-cells defined by production of IL-17 and IL-22, appear to be increased in number but decreased in activity in AD (unlike psoriasis). Guidelines of care for the management of atopic dermatitis: Section 3. Dysbiosis and Staphylococcus aureus Colonization Drives Inflammation in Atopic Dermatitis. 2011, 25 (Suppl. Surg. Previously, therapeutic options for AD and psoriasis, particularly extensive and/or severe disease, were limited to topical and non-targeted systemic immunosuppressants that had poor efficacy, safety and/or tolerability. Atopic eczema and domestic water hardness. 2019, 139, 583–590. [Google Scholar] [CrossRef]Leung, D.Y.M.; Boguniewicz, M.; Howell, M.D.; Nomura, I.; Hamid, Q.A. New insights into atopic dermatitis. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. 2013, 169, 137–145. 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Impaired tight junctions obstruct stratum corneum formation by altering polar lipid and profilaggrin processing. Nature 2007, 445, 648–651. 2012, 91, 552–566. Science 2003, 300, 1527–1528. In combination with TCS, tazarotene shows increased potency and decreased local AEs [174,175].Phototherapy is a therapeutic option for moderate-to-severe psoriasis involving a large BSA (>10%), both as monotherapy and combination therapy. [Google Scholar] [CrossRef]Thyssen, J.P.; McFadden, J.P.; Kimber, I. 2019, 139, 1063–1072. 2014, 134, 993–999, discussion 1000. 2011, 365, 1315–1327. 2015, 135, 3183–3186. Historically, treatment for psoriasis was limited to topical preparations of anthralin (also known as dithranol), which induces apoptosis of keratinocytes through production of reactive oxygen species, and coal tar, which inhibits production of IL-15 and nitric oxide [163,164]. Fine mapping major histocompatibility complex associations in psoriasis and its clinical subtypes. 2011, 127, 773–786.e7. [Google Scholar] [CrossRef]Angelova-Fischer, I.; Dapic, I.; Hoek, A.-K.; Jakasa, I.; Fischer, T.W.; Zillikens, D.; Kezic, S. Oral tofacitinib is currently an FDA-approved therapy for psoriatic arthritis [217,218], and has shown promising findings for the treatment of psoriasis in phase III double-blind, placebo controlled RCTs (PASI-75 at week 16: 40–59%) [219,220]. 2017, 34, 528–534. [Google Scholar] [CrossRef]Reich, K.; Gooderham, M.; Thaçi, D.; Crowley, J.J.; Ryan, C.; Krueger, J.G.; Tsai, T.-F.; Flack, M.; Gu, Y.; Williams, D.A.; et al. Both are associated with similar AEs that restrict their use in children, including diarrhea, nausea, vomiting, anemia, leukopenia, immune suppression, and increased risk of infection. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (. Semin. 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The results of phase III studies are pending.IL-4, IL-13, IL-31, and other important cytokines in the pathogenesis of AD signal through extracellular receptors that activate intracellular Janus kinases (JAKs) [109,110]. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. 2016, 136, 2192–2200. 2017, 76, 405–417. 2013, 169, 412–416. While effective in the short-term and as a bridge therapy, their long-term use is limited by a poor AE profile including hyperglycemia, diabetes, weight gain, insomnia, cardiovascular disease, osteoporosis and osteonecrosis, adrenal insufficiency, gastroesophageal reflux, and immune suppression [93,94]. 2009, 9, 556–567. [Google Scholar] [CrossRef]Papp, K.A.; Menter, M.A.; Abe, M.; Elewski, B.; Feldman, S.R.; Gottlieb, A.B.; Langley, R.; Luger, T.; Thaci, D.; Buonanno, M.; et al. [Google Scholar] [CrossRef]Baurecht, H.; Irvine, A.D.; Novak, N.; Illig, T.; Bühler, B.; Ring, J.; Wagenpfeil, S.; Weidinger, S. 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Adjunctive treatment with topical vitamin D analogs in children with psoriasis is overall very well tolerated with minimal cutaneous AEs and extremely rare systemic AEs (e.g., hypercalcemia, hypercalciuria) with overuse. Nature 2007, 449, 564–569. [Google Scholar] [CrossRef]Mehta, D.; Lim, H.W. Ultraviolet B Phototherapy for Psoriasis: Review of Practical Guidelines. Skin pH Is the Master Switch of Kallikrein 5-Mediated Skin Barrier Destruction in a Murine Atopic Dermatitis Model. 2015, 173, 1387–1399. Your doctor may use "atopic dermatitis" and "eczema" interchangeably, or they may just use one term or the other to describe your condition. NB-UVB has a good safety profile with a low risk for cutaneous malignancy. [Google Scholar] [CrossRef] [PubMed]Riethmuller, C.; McAleer, M.A.; Koppes, S.A.; Abdayem, R.; Franz, J.; Haftek, M.; Campbell, L.E.; MacCallum, S.F.; McLean, W.H.I.; Irvine, A.D.; et al. 2010, 207, 2921–2930. Psoriasis and the metabolic syndrome. 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Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). 2010, 42, 996–999. Primers 2016, 2, 16082. Sci. [Google Scholar] [CrossRef]Mócsai, G.; Gáspár, K.; Nagy, G.; Irinyi, B.; Kapitány, A.; Bíró, T.; Gyimesi, E.; Tóth, B.; Maródi, L.; Szegedi, A. [Google Scholar] [CrossRef]Dvorakova, V.; O'Regan, G.M.; Irvine, A.D. Methotrexate for Severe Childhood Atopic Dermatitis: Clinical Experience in a Tertiary Center. [Google Scholar] [CrossRef] [PubMed]Eichenfield, L.F.; Call, R.S.; Forsha, D.W.; Fowler, J.; Hebert, A.A.; Spellman, M.; Stein Gold, L.F.; Van Syoc, M.; Zane, L.T.; Tschen, E. Dis. Enhanced meta-analysis and replication studies identify five new psoriasis susceptibility loci. 2007, 21, 606–619. 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TCS use in children is sometimes limited given concern for cutaneous (e.g., atrophy, fragility, striae, infection) and systemic (e.g., hypothalamic–pituitary axis suppression) AEs. While TCIs do not cause atrophy or hypothalamic–pituitary axis suppression, they are associated with application site reactions such as burning or stinging and a theoretical black-box warning by the United States Food and Drug Association for malignancy. [Google Scholar] [CrossRef] [PubMed]Papp, K.A.; Reich, K.; Paul, C.; Blauvelt, A.; Baran, W.; Bolduc, C.; Toth, D.; Langley, R.G.; Cather, J.; Gottlieb, A.B.; et al. [Google Scholar] [CrossRef] [PubMed]De Korte, J.; Sprangers, M.A.; Mombers, F.M.; Bos, J.D. Quality of life in patients with psoriasis: A systematic literature review. Children 2019, 6(10), 108; Received: 30 August 2019 / Revised: 23 September 2019 / Accepted: 25 September 2019 / Published: 4 October 2019 Atopic dermatitis (AD) and psoriasis are chronic inflammatory skin diseases associated with a significant cutaneous and systemic burden of disease as well as a poor health-related quality of life. 2008, 58, 106–115. 2014, 371, 326–338. 2016, 74, 841–850. [Google Scholar] [CrossRef]Papp, K.A.; Krueger, J.G.; Feldman, S.R.; Langley, R.G.; Thaçi, D.; Torii, H.; Tyring, S.; Wolk, R.; Gardner, A.; Mebus, C.; et al. Discoid eczema: This type usually happens on the lower legs and forearms. However, further studies are needed to better understand crisaborole's efficacy in children, especially in comparison with TCS and TCIs. Common AEs of crisaborole in children include application site burning and/or stinging and, rarely, application site skin infection. Pustular psoriasis, occurring in both local and generalized forms, presents with innumerable, coalescing, sterile pustules. The IL-17 family is composed of six members, two of which (IL-17A and IL-17F) appear to be most relevant in psoriasis. Eur. Data supporting their use in monotherapy and/or combination therapy is derived from years of anecdotal clinical experience and studies performed in adults, as RCTs are for these agents are rare in children, especially under the age of 12. [Google Scholar] [CrossRef]Parisi, R.; Symmons, D.P.M.; Griffiths, C.E.M.; Ashcroft, D.M.; The Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) Project Team. [Google Scholar] [CrossRef]Fluhr, J.W.; Kao, J.; Jain, M.; Ahn, S.K.; Feingold, K.R.; Elias, P.M. Generation of free fatty acids from phospholipids regulates stratum corneum acidification and integrity. [Google Scholar] [CrossRef]Weidinger, S.; Beck, L.A.; Bieber, T.; Kabashima, K.; Irvine, A.D. Atopic dermatitis. 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Functional impairment of tight junctions has been observed in patients with AD and results in skin-barrier dysfunction [53,54,55].A variety of external and environmental factors have also been shown to contribute to skin-barrier impairment in AD patients, including in utero exposures [56], bacterial dysbiosis [57], harsh climate [58], water hardness [59,60], airborne pollutants [61,62,63], tobacco smoke [64], personal care products (i.e., irritants and pruritogens) [65,66,67], and, in certain cases, contact allergens [68]. 2006, 38, 441–446. [Google Scholar] [CrossRef] [PubMed]Schmitt, J.; Schmitt, N.; Meurer, M. 2017, 13, 15–26. [Google Scholar] [CrossRef]Simpson, E.L.; Imafuku, S.; Poulin, Y.; Ungar, B.; Zhou, L.; Malik, K.; Wen, H.-C.; Xu, H.; Estrada, Y.D.; Peng, X.; et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. Lancet 2017, 390, 40–49. The risk of melanoma in association with long-term exposure to PUVA. Stress can also be a trigger. Following keratinocyte damage, two important events occur to activate the innate immune system: (1) keratinocytes dramatically upregulate the production of AMPs including S100, β-defensins, and LL-37 (i.e., cathelicidin), and (2) damaged keratinocytes release DNA, RNA, and other endogenous danger signals [117,118]. Severe skin inflammation and filaggrin mutation similarly alter the skin barrier in patients with atopic dermatitis. Atopic Dermatitis Is an IL-13-Dominant Disease with Greater Molecular Heterogeneity Compared to Psoriasis. [Google Scholar] [CrossRef]Thaçi, D.; Simpson, E.L.; Beck, L.A.; Bieber, T.; Blauvelt, A.; Papp, K.; Soong, W.; Worm, M.; Szepietowski, J.C.; Sofen, H.; et al. Plaque psoriasis is characterized by well-demarcated, erythematous, scaly plaques on the trunk and extensor surfaces of the limbs. [Google Scholar] [CrossRef] [PubMed]Gordon, K.B.; Langley, R.G.; Leonardi, C.; Toth, D.; Menter, M.A.; Kang, S.; Heffernan, M.; Miller, B.; Hamlin, R.; Lim, L.; et al. Overall, it appears to be less effective than traditional systemic agents for plaque psoriasis, and has several important AEs including dry skin and mucous membranes, dyslipidemia, elevated liver function tests, and potential teratogenicity [181].In 2014, the FDA approved apremilast for the treatment of moderate-to-severe psoriasis. Your doctor may suggest using steroids in combination with ultraviolet (UV) light therapy. [Google Scholar] [CrossRef] [PubMed]Novak, N.; Kruse, S.; Potreck, J.; Maintz, L.; Jenneck, C.; Weidinger, S.; Fimmers, R.; Bieber, T. Am. Acad. Rev. [Google Scholar] [CrossRef]Allen, M.H.; Veal, C.; Faassen, A.; Powis, S.H.; Vaughan, R.W.; Trembath, R.C.; Barker, J.N. A non-HLA gene within the MHC in psoriasis. [Google Scholar] [CrossRef] [PubMed]Allen, M.H.; Ameen, H.; Veal, C.; Evans, J.; Ramrakha-Jones, V.S.; Marsland, A.M.; Burden, A.D.; Griffiths, C.E.M.; Trembath, R.C.; Barker, J.N.W.N. The major psoriasis susceptibility locus PSORS1 is not a risk factor for late-onset psoriasis. It usually happens on the palms of the hands and soles of the feet. Th22 cells, a more recently described subset of T-cells that show an increased number and activity in AD lesions, produce high levels of IL-22 that may induce epidermal hyperplasia and terminal keratinocyte differentiation [89].Topical therapies are typically the first-line treatment modality for AD. Secukinumab in plaque psoriasis--results of two phase 3 trials. [Google Scholar] [CrossRef]Perkin, M.R.; Craven, J.; Logan, K.; Strachan, D.; Marrs, T.; Radulovic, S.; Campbell, L.E.; MacCallum, S.F.; McLean, W.H.I.; Lack, G.; et al. Psoriasis: A possible risk factor for development of coronary artery calcification. 2018, 78, 733–740. Genetic polymorphisms in Toll-like receptors (TLRs), one such family of PRRs, confers increased risk of AD and staphylococcus aureus (SA) infection [76,77]. Carbazole is a naturally occurring inhibitor of angiogenesis and inflammation isolated from antipsoriatic coal tar. [Google Scholar] [CrossRef] [PubMed]Elder, J.T. Genome-wide association scan yields new insights into the immunopathogenesis of psoriasis. Association between domestic water hardness, chlorine, and atopic dermatitis risk in early life: A population-based cross-sectional study. Photo Courtesy: JGI/Jaime Grill/Getty Images There's no cure for atopic dermatitis. You can also work with your doctor to figure out what triggers your symptoms. Lancet 2008, 371, 1675–1684. Inverse psoriasis affects the intertrigenous skin with erythematous, occasionally erosive patches and plaques. 2016, 16, 15. [Google Scholar] [CrossRef]Gordon, K.B.; Blauvelt, A.; Papp, K.A.; Langley, R.G.; Luger, T.; Ohtsuki, M.; Reich, K.; Amato, D.; Ball, S.G.; Braun, D.K.; et al. 2019, 58, 649–658. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). 2009, 34, 295–298. Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. [Google Scholar] [CrossRef]Jimenez, J.L.; Punzón, C.; Navarro, J.; Muñoz-Fernández, M.A.; Fresno, M. [Google Scholar] [CrossRef] [PubMed]Paul, C.; Cather, J.; Gooderham, M.; Poulin, Y.; Mrowietz, U.; Ferrandiz, C.; Crowley, J.; Hu, C.; Stevens, R.M.; Shah, K.; et al. 2015, 73, 395–399. 2010, 29, 10–15. Common variants at TRAF3IP2 are associated with susceptibility to psoriatic arthritis and psoriasis. [Google Scholar] [CrossRef]Yu, S.H.; Attarian, H.; Zee, P.; Silverberg, J.I. Burden of Sleep and Fatigue in US Adults With Atopic Dermatitis. 2008, 25, 184–188. [Google Scholar] [CrossRef]Morizane, S.; Gallo, R.L. Antimicrobial peptides in the pathogenesis of psoriasis. Numerous RCTs demonstrated clinical efficacy for both continuous and intermittent treatment of psoriasis with varying potencies of TCS [165,166]. [Google Scholar] [CrossRef]Silverberg, J.I. Adult-Onset Atopic Dermatitis. [Google Scholar] [CrossRef]Landells, I.; Marano, C.; Hsu, M.-C.; Li, S.; Zhu, Y.; Eichenfield, L.F.; Hoeger, P.H.; Menter, A.; Paller, A.S.; Taïeb, A.; et al. However, the role of IL-17 inhibition in flaring inflammatory bowel disease (IBD) in those with a personal or family history of IBD is currently under investigation [208].Based on clinical data from ustekinumab patients in conjunction with basic studies showing protective effects of IL-12 in psoriasis [209] and a more important role for IL-12 in Th1 mediated host defense, IL-23 was identified as a more specific target for psoriasis therapy [210]. The era for personalized medicine in AD and psoriasis is upon us! Data curation, R.C. and J.I.S.; Formal analysis, R.C. and J.I.S.; Writing—original draft, R.C. and J.I.S.; Writing—review and editing, R.C. and J.I.S.This research received no external funding. While psoriasis can manifest with a variety of morphologies, all subtypes share several important features: (1) hyperplasia of the epidermis (i.e., acanthosis), (2) incomplete keratinization with retention of nuclei (i.e., parakeratosis), (3) newly generated, tortuous superficial blood vessels (i.e., neovascularization), and (4) a dense inflammatory infiltrate composed of DCs, macrophages, neutrophils, and T-cells [116].The initiation phase of psoriasis consists of an external insult to the epidermis, such as trauma (e.g., Koebner phenomenon), medication (e.g., β-blocker, ACE-inhibitor, lithium), and/or infection (e.g., group A streptococcus) [115]. In general, biologic treatment-associated AEs in children with psoriasis are similar to those observed in adults and more favorable compared to classic systemic therapies. Photo Courtesy: Engdao Wichitpunya/EyeEm/Getty Images Atopic dermatitis is just one type of eczema. [Google Scholar] [CrossRef] [PubMed]Tsoi, L.C.; Spain, S.L.; Knight, J.; Ellinghaus, E.; Stuart, P.E.; Capon, F.; Ding, J.; Li, Y.; Tejasvi, T.; Gudjonsson, J.E.; et al. Safety and efficacy of a fixed combination of halobetasol and tazarotene in the treatment of moderate-to-severe plaque psoriasis: Results of 2 phase 3 randomized controlled trials. [Google Scholar] [CrossRef] [PubMed]Arbiser, J.L.; Govindarajan, B.; Battle, T.E.; Lynch, R.; Frank, D.A.; Ushio-Fukai, M.; Perry, B.N.; Stern, D.F.; Bowden, G.T.; Liu, A.; et al. Exp. [Google Scholar] [CrossRef] [PubMed]Nemoto, O.; Furue, M.; Nakagawa, H.; Shiramoto, M.; Hanada, R.; Matsuki, S.; Imayama, S.; Kato, M.; Hasebe, I.; Taira, K.; et al. [Google Scholar] [CrossRef] [PubMed]Guttman-Yassky, E.; Lowes, M.A.; Fuentes-Duculan, J.; Whynot, J.; Novitskaya, I.; Cardinale, I.; Haider, A.; Khatcherian, A.; Carucci, J.A.; Bergman, R.; et al. [Google Scholar] [CrossRef]Schulz, F.; Marenholz, I.; Fölster-Holst, R.; Chen, C.; Sternjak, A.; Baumgrass, R.; Esparza-Gordillo, J.; Grüber, C.; Nickel, R.; Schreiber, S.; et al. 2000, 80, 188–191. 2009, 123, 1244–1252. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. [Google Scholar] [CrossRef]Kaur, I.; Dogra, S.; De, D.; Kanwar, A.J. Systemic methotrexate treatment in childhood psoriasis: Further experience in 24 children from India. Atopic dermatitis is a type of skin irritation that's more common in children and people with allergies. Dermatitis 2018, 29, 270–277. [Google Scholar] [CrossRef]Rendon, A.; Schäkel, K. 2019, 119, e3. Patients with AD have significantly higher pH in both lesional and non-lesional skin [50,51].Tight junctions are epidermal protein complexes composed of claudins and occludins that are designed to seal off intercellular space, control permeability to solutes, water, pathogens, antigens, and allergens, and maintain cell polarity [52]. Despite these potential AEs, both TCS and TCIs can be used safely and efficaciously in continuous and/or intermittent fashion. [Google Scholar] [CrossRef] [PubMed]Menter, A.; Tyring, S.K.; Gordon, K.; Kimball, A.B.; Leonardi, C.L.; Langley, R.G.; Strober, B.E.; Kaul, M.; Gu, Y.; Okun, M.; et al. More recently, next-generation sequencing and expression profiling have been combined with linkage and association studies to identify genetic variants with high accuracy, as evidenced by the successful identification of loss-of-function mutation in IL-36 antagonist (IL-36N) as the genetic basis for generalized pustular psoriasis [161,162].As with AD, topical therapies are the first-line treatment for psoriasis, both as monotherapy in mild-to-moderate disease and as combination therapy with oral systemic, biologic, and phototherapy in moderate-to-severe disease. Once you know what causes flares, you can make a plan to avoid these things and get your symptoms under control. [Google Scholar] [CrossRef] [PubMed]Yin, X.; Low, H.Q.; Wang, L.; Li, Y.; Ellinghaus, E.; Han, J.; Estivill, X.; Sun, L.; Zuo, X.; Shen, C.; et al. 2007, 119, 1210–1217. 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