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Efficacy and safety of adalimumab treatment in psoriasis with psoriatic arthritis: Result from post-marketing surveillance in Japan

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The TNF-α antagonist adalimumab (ADA) has been used to treat patients (pts) with moderate to severe plaque psoriasis (Ps) and psoriatic arthritis (PsA) in Japan. This analysis assessed efficacy and safety of ADA treatment in pts with PsA from post-marketing surveillance. This 24-week (wk), open-label, post-marketing, observational trial was conducted at 634 sites in Japan (NCT01155570) in pts with Ps and with or without PsA. In PsA pts, efficacy evaluations included the proportion of pts achieving ≥75% reduction in Psoriasis Area Severity Index (PASI) from baseline (PASI75; LOCF), Disease Activity Score 28 (DAS28; observed cases), and European League Against Rheumatism (EULAR; LOCF) response (moderate, good); safety was also assessed. Of registered Ps pts (n=749; excluding 3 from 1 site), 217 and 213 pts with PsA were evaluated for safety and efficacy, respectively, of which 146 (67.3%) were men. Pts mean age was 47.9±12.0 years and mean disease (Ps or PsA) duration 13.3±9.8 years; 97.2% had previous Ps or PsA treatment. PASI75, evaluated in 156 PsA pts, was achieved by 45.2% and 51.3% at wks16 and 24, respectively. Mean DAS28-erythrocyte sedimentation rate, evaluated in 94 pts, improved from 4.4±1.7 at baseline to 2.4±1.3 (n=60) at wk16 and 2.3±1.3 (n=62) at wk24 (p<0.0001, both). Mean DAS28-C-reactive protein, evaluated in 131 pts, improved from 3.5±1.3 at baseline to 2.0±1.0 (n=81) at wk16 and 1.8±0.9 (n=85) at wk24 (p<0.0001, both). EULAR response (good/moderate), evaluated in 113 pts, was 7.1%/65.5% at wk16 and 8.9%/68.1% at wk24. Adverse events (AEs) were reported by 82 (37.8%) pts; serious AEs by 9 (4.1%). Following ADA treatment in Japanese pts with PsA, no new AEs or new incidences of AEs were observed; PASI, DAS28 and EULAR response improved significantly from baseline to wks 16 and 24.

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Similarity in survival in stage 4 basosquamous carcinoma and stage 4 squamous cell carcinoma: Results of a single-site retrospective cohort study

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Basosquamous carcinoma (BSC) is a rare histological subtype of basal cell carcinoma (BCC) thought to have a clinical course more similar to squamous cell carcinoma (SCC). However, no estimates of overall survival (OS) or progression-free survival (PFS) are currently available for BSC of any stage, making direct comparison impossible. The objective of this single-institution retrospective cohort study was to estimate and compare OS and PFS of Stage 4 BSC and Stage 4 SCC, as well as to relate these values to published estimates of OS and PFS of Stage 4 BCC. Biopsy-proven cases were identified by querying an institutional cancer registry, yielding 18 Stage 4 BSC and 36 Stage 4 SCC cases. The median OS (95% confidence interval (CI)) was 6.5 (3.9-∞) years for BSC and 3.5 (1.8-5.7) years for SCC. The five-year OS rate (95% CI) was 53% (19-79%) for BSC and 30% (14-49%) for SCC. The median PFS (95% CI) was 1.2 (0.5-3.0) years for BSC and 0.7 (0.5-1.0) years for SCC. Cox models adjusting for age at Stage 4 diagnosis and nodal status revealed a hazard ratio (95% CI) of 0.77 (0.32-1.85) for OS and 0.86 (0.43-1.73) for PFS of BSC compared to SCC. Log-rank tests for differences in OS (p=0.15) and PFS (p=0.53) between BSC and SCC were not statistically significant. Our study is the first to report survival data for BSC. While the OS and PFS of BSC and SCC are not significantly different in this study, the survival curves do show that BSC carries an intermediate prognosis compared to BCC and SCC. This suggests that larger studies may reveal statistically significant differences in OS and PFS between BSC and SCC.

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Free dermatoplasty combining with vacuum sealing drainage with or without Pelnac used for the treatment of extensive follicular occulusion triad in the gluteal and perianal regions

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INTRODUCTION: Follicular occulusion triad is a chronic suppurative disease having a great impact on quality of life. In this study, we present extensive follicular occulusion triad cases with their respective treatment and outcomes. METHODS: A retrospective review of the medical records from January 1998 to December 2012 of 21 patients was performed. RESULTS: Twenty-one patients with extensive follicular occulusion triad in the gluteal and perianal regions underwent total surgical excision. All patients were male and had a total number of 57 operations. The median operation time was 2.7 times. The wound was left open for secondary healing in 16 cases, and the mean time for fully healing was 4.3 weeks (range: 2.7-9.4 weeks). 12 patients with large-area skin defects ranged from 8×12 to 25×37 cm2 were treated by free mesh dermatoplasty combining with Vacuum sealing drainaging (VSD) after surgical excision. Pelnac was placed onto the skin defect after removal of the lesion in 4 patients. Two weeks postoperatively, the silicone film was peeled off and a thin split-thickness skin graft was placed on the regenerated dermis-like connective tissues. In this group, it took 2 months in total to heal the wound completely. In addition, three patients achieved primary wound closure by using mesh skin grafting, the other two by rotation flaps. Successful treatment without recurrence was accomplished in 17 (80.9%) of the patients. CONCLUSION: Conservative treatment methods have little or no effect on extensive perineal/perianal follicular occulusion triad. The only successful treatment was wide surgical excision. Management of the wound after wide excision should be tailored to the individual patient. Free dermatoplasty combining with VSD with or without Pelnac used for the treatment of large-area soft tissue defects maybe a simple, fast and effective treatment method.

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The effect of conditioned media of adipose-derived stem cells on wound healing after ablative fractional carbon dioxide laser resurfacing

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To evaluate the benefits of conditioned medium of Adipose-derived stem cells (ADSC-CM) on wound healing after Fractional carbon dioxide laser resurfacing (FxCR) on human skin. Nineteen subjects were treated with FxCR on the bilateral inner arms. ADSC-CM was applied on FxCR site of one randomly selected arm. Transepidermal water loss (TEWL), skin color, and gross-elasticity of FxCR site on both arms were measured. Skin samples were taken by biopsy from three subjects 3 weeks after treatment for histopathological manifestations and mRNA expressions of procollagen types I and III, elastin genes were noted. The index of erythema, melanin, and TEWL of the ADSC-CM-treated skin were significantly lower than those of the control side. The mRNA expression of type III procollagen in ADSC-CM-treated group at 3 weeks post-treatment was 2.6 times of that of control group. Application of allograft ADSC-CM is an effective method for enhancing wound healing after FxCR, by reducing transient adverse effects such as erythema, hyperpigmentation, and increased TEWL.

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Leukemia cutis patients with AML demonstrate comparable survival to the general AML population and long-term survival when treated with stem cell transplantation

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Leukemia cutis refers to skin infiltration by lymphoid or myeloid malignant cells, and is considered a poor prognostic factor in patients with hematologic malignancy. However, studies of the disease are limited, especially over the past decade despite major advancements in chemotherapeutics and stem cell transplantation. We hypothesized that leukemia cutis is not a poor prognostic factor in AML. To study this, we performed a retrospective study of patients ≥ 18 years old with histopathologic diagnosis of leukemia cutis over 12 years at Brigham and Women's Hospital/Dana Farber Cancer Institute. We identified 51 patients with acute myelogenous leukemia (AML) with leukemia cutis. Duration of survival for all AML patients with leukemia cutis was 22 months, with absolute survival rate of 36% and 24% at 1- and 5-years, respectively, comparable to the current national 5-year survival rate in AML of 24.9%. Survival in leukemia cutis patients varied with type of AML. Further, leukemia cutis patients who were treated with stem cell transplantation had significantly prolonged survival of mean duration 44 months, with absolute 1- and 5-year survival rates of 69 and 46%, respectively, compared to only 7 months mean survival, and 1- and 5-year survival rates of 10 and 0%, respectively, in non-transplanted patients with leukemia cutis. In conclusion, our data suggests that leukemia cutis may not be the poor prognostic factor that it was previously thought to be and stem cell transplantation can lead to improved survival in this patient population.

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Cyclosporine A treatment in atopic dermatitis results in suppression of Th2/Th22 inflammation and epidermal pathology

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Atopic dermatitis (AD) is the most common inflammatory skin disease. Evolving disease models link changes in epidermal differentiation to Th2/Th22 cytokine activation. However, these models have not been tested by in-vivo suppression of T-cell cytokines. Cyclosporine A (CsA) is an effective treatment for severe disease, but its mechanism in AD lesions has not been studied. We aimed to establish the ability of a systemic immune-suppressant to modulate immune and epidermal alterations that form the pathogenic disease phenotype and to correlate changes with clinical improvement. The effects of CsA on AD skin pathology were evaluated using gene-expression and immunohistochemistry studies in baseline, week 2 and 12 lesional and non-lesional biopsies from 19 patients treated with 5 mg/kg/d CsA. After 2 and 12 weeks of treatment, reductions of 50.89% and 73.44% in Scoring of AD/SCORAD were seen. Clinical improvements were associated with significant genomic changes in lesional but also non-lesional skin, particularly reductions of Th2, Th22, and some Th17-related molecules (i.e IL-13, IL-22, CCL17, CCL18, S100A7-9, PI3), and modulation of epidermal hyperplasia and differentiation markers (K16, LOR, FLG, PPL). This is the first study that establishes a link between Th2/Th22 cytokines and molecular epidermal alterations as well as correlations between clinical improvement and skin biomarkers. The reversal of the molecular phenotype with CsA and the associated disease response biomarkers can serve as a reference for the successful modulation of tissue inflammation with specific immune-antagonists in future studies, contributing to the understanding of the specific cytokines involved in epidermal pathology.

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Impact of ixekizumab on blood neutrophil levels and the incidence of infections caused by candida albicans or staphylococcus aureus

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IL-17A homodimers and IL-17A/F heterodimers play important roles in neutrophil recruitment and protection against extracellular pathogens such as C. albicans and S. aureus. Ixekizumab, a monoclonal antibody directed against IL-17A, is currently in development for treating plaque psoriasis. In this analysis, using data from an open-label extension of a previously reported phase 2 study (1), the impact of ixekizumab treatment on blood neutrophil levels and the incidence of candidal and staphylococcal infections were assessed. In an open-label manner, 120 patients received 120 mg of ixekizumab subcutaneously every 4 weeks. Safety data were available through Week 52 for all patients; additional data for some patients were available through Week 100. Incidence of neutropenia was graded according to CTCAE criteria. Candidal and staphylococcal infections were as reported by the investigator and microbiologic confirmation was not required. Among all 120 patients, 4 patients experienced transient grade 1 neutropenia that were not clinically significant; no grade 2 or grade 3 neutropenia occurred. Overall, 49 patients experienced a treatment-emergent infection of any kind. Five of these 49 had a reported candidal (4 oral and 1 vulvovaginal), 1 patient had a vulvovaginal infection due to an unspecified yeast and 2 had a reported staphylococcal infection (ear infection and impetigo), all of which resolved with proper treatment and did not interfere with ixekizumab dosing. None of these patients had concurrent neutropenia. In this study there was a low incidence of neutropenia, which was transient and not severe in psoriasis patients treated for 1 year with ixekizumab. Unlike what may have been expected based upon mechanism of action, ixekizumab treatment was associated with a low frequency of candidal or staphylococcal infections. Further study is needed to fully understand the impact of ixekizumab treatment on circulating neutrophil levels and host defense.

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A single application of acyclovir mucoadhesive buccal tablet reduces recurrence of herpes labialis in a randomized double-blind phase 3 study: Exploratory results

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Objectives: Acyclovir mucoadhesive buccal tablet (ABT), is an innovative drug delivery system that provides high sustained-release local exposure to acyclovir in oral mucosa. ABT 50mg was reported in the LIP study to significantly reduce the time to healing (TTH) of vesicular lesions and increase the incidence of aborted episodes of herpes labialis (HL) . A secondary endpoint was to examine incidence and time to next recurrence of HL. Methods: In a randomized, multicenter, phase 3, double-blind, placebo-controlled study, 775 patients, (378 in the ABT group and 397 in the placebo group), with at least 4 recurrent HL lesions per year were treated. Participants self-applied a single ABT 50mg or placebo tablet as soon as prodromal symptoms occurred. 537 patients, 267 patients ABT and 270 placebo, agreed to participate in a 9-month follow-up for the evaluation for assessing whether one single dose administration of ABT could have an impact on incidence and time to the next recurrence of HL (TTR). Results: Following a single application of ABT 50mg or placebo during the HL episode, a HL episode recurred during the 9-month follow up period in 64.2% of patients treated with ABT50mg vs 73.6% in the placebo group (p=0.027). The mean TTR in the ABT 50mg group (304±19.4 days) was significantly longer than that of the placebo group (199±9.3 days, Δ=105 days, Logrank test p=0.042). Good safety and tolerability were found in both ABT 50mg and placebo groups. Conclusions: A single application of ABT 50 mg during the prodromal symptoms of HL reduces the incidence of the next recurrence and delays the recurrence of next herpes episodes. Thus ABT 50mg may modify the clinical course of labial herpes.

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Off-target effects of BRAF inhibitors: Roles in SCC induction and the relationship to paradoxical ERK signaling

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B/RAF inhibitors are known to induce cutaneous squamous cell carcinomas (cSCC) in patients, an effect ascribed to paradoxical ERK activation. We recently reported that the RAF inhibitors vemurafenib and sorafenib potently suppress JNK-mediated apoptosis through the off-target inhibition of ZAK (PMID: 24192036, 24170769), demonstrating this as an independent mechanism accounting for 20-40% of the total tumor-promoting effect of these drugs. However, it is not known why B/RAF inhibitors differ substantially in their ability to induce cSCC. Sorafenib and vemurafenib, but not dabrafenib or LGX818, bind and inhibit ZAK at clinically relevant doses, leading to inhibition of JNK activation. We show that ZAK primarily activates JNK1 to initiate apoptosis using a chemical genetic approach with covalent small molecule inhibitors of JNK. Surprisingly, ZAK is also required for apoptosis following MEK or BRAF inhibition in BRAF-mutant melanoma cells. Our results show that RAF inhibitors should be counterscreened against activators of JNK1, including ZAK, to avoid countervailing off-target effects. There are also major differences in the ability of B/RAF inhibitors (sorafenib, dabrafenib, LGX818, PLX4720, paradox breakers) to activate ERK signaling in BRAF wild-type cells. Using a novel fluorescent kinase activity probe, we show that all of these inhibitors exhibit paradoxical ERK activation, but not always at clinically relevant doses, with widely varying magnitudes and lengths of activation, from a few hours to over 72 hours. Taken together, our results show that the paradoxical and off-target effects of B/RAF inhibitors have potent biologic effects that can account for differences in the frequency of adverse events such as cSCC, suggesting that the design of kinase inhibitors must incorporate a detailed understanding of these effects.

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Risk of rash associated with panitumumab in cancer patients: A systematic review of the literature and meta-analysis

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Panitumumab (Pan) is indicated as a single agent for the treatment of epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal carcinoma (mCRC). The incidence and risk of rash have been reported, however they have been inconsistent in published trials. We conducted a systematic review and meta-analysis of the literature to determine the incidence and risk of developing rash. We searched PubMed (1998-2013), ASCO Conferences (2004-2013) and Web of Science (1998-2013) databases. Eligible studies were limited to randomized controlled trials in which patients received Pan doses of 6 mg/kg every 14 days (Q2W). Incidence, relative risk (RR), and 95% confidence intervals (CI) were calculated using random-effects and fixed-effects models based on heterogeneity of included studies. Data from 6 randomized controlled trials with a total of 2,053 patients treated with Pan were available for analysis. The overall incidence of all-grade rash for Pan was 71.3% (95%CI: 42.3% - 35.5%) while for controls was 5.6% (95%CI: 1.7%- 17.1%). The overall incidence of high-grade (grade ≥3) skin rash for Pan was 28.2% (95%CI: 21.5%-36%) compared to 1.4% (95% CI: 0.8%-2.3%) for controls group. Pan was associated with increased risk of all-grade rash (RR=10.5, 95%CI: 4.7%-23.5%; P<0.001) when compared to controls. The risk of high-grade rash was also increased (RR=22.4, 95%CI: 14.8%-33.9%; P<0.001). Patients with mCRC who are treated with panitumumab are at significantly greater risk for developing rash, especially high-grade rash. Further studies for prevention and treatment of this toxicity are needed in order to maintain patient's quality of life and minimize the need for dose modification, all of which may impact clinical outcome.

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Interventions for management of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in the human immunodeficiency virus (HIV) population: A systematic literature review

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Although SJS and TEN are rare and potentially life-threatening, anti-HIV drugs pose a higher risk of these reactions, and there exists no evidence-based assessment of treatments for these reactions in the HIV-positive population. We conducted a systematic review of literature for intervention and outcome of SJS and TEN in the HIV-positive population. We searched Ovid Medline, Cochrane Central Register of Controlled Trials, Scopus, and EMBASE databases (1980-June 2013). Search criteria included HIV-positive individuals, a diagnosis of drug-induced SJS or TEN and a stated intervention with outcome (living or deceased). The search generated 908 total reports, 89 of which were evaluable and which represented 565 patients. Only case reports, case series and observational studies constituted the evaluable reports, for which there were 7 categories of interventions. Despite insufficient data to provide high-level evidence-based recommendations for interventions in HIV-positive individuals with SJS or TEN, our findings are consistent with those of the general population: immediate discontinuation of the inciting drug(s) is an advisable intervention in all cases. Furthermore, the available evidence supports discontinuation of inciting drug(s) plus medicated skin-directed therapies and supportive care as additional categories of intervention in the management and successful outcome for HIV-positive patients with SJS/TEN. Moreover, our findings suggest that systemic corticosteroid use, alone or in combination with other interventions, did not significantly change survival. Further investigations are needed to determine optimal management of SJS and TEN in the HIV-positive population.

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Cutaneous ATLL is a diagnostic challenge and has heterogenous clinical and histologic features

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Adult T-cell leukemia/lymphoma (ATLL) patients with skin involvement are not well studied in the United States. The objective was to characterize clinical and histologic features of ATLL patients with cutaneous disease. 53 patients [17 skin-first (SF), 8 skin-second (SS), and 29 skin-uninvolved (SU)] seen at MSKCC from 1998 to 2013 were identified, of which 46% (n=25) had skin involvement. SF were primarily of Caribbean origin (94%) and had a median symptom duration of 11.9 months (vs. 1.9 months for SS+SU, P < 0.001). Median overall survival in SF appeared significantly longer compared to SS+SU (26.7 vs. 10.0 months, P <0.001), but no difference remained when stratified by Shimoyama subtype. In SF, 11 died, 4 were lost to f/u, and 2 were alive at last f/u. Fifteen patients (88%) were evaluated by a dermatologist before ATLL diagnosis, with 5 (33%) correctly diagnosed. 32 clinical diagnoses were considered, with mycosis fungoides (MF) (n=9), Sézary syndrome (n=3), and dermatophytoses, psoriasis, drug rash, and eczema (each n=2) most common. After skin biopsy, 14/17 (82%) received an initial clinicopathologic diagnosis other than ATLL, most commonly MF (n=8). Caribbean origin (35%) and an unusual clinical presentation (29%) were the most common clues for clinicians to suspect ATLL. Predominant lesion morphology at diagnosis was nodules (35%), followed by plaques (24%), papules (24%), patches (12%), and erythroderma (6%). 43 skin biopsies from 22 patients revealed notable findings, including large cell morphology (70%), epidermotropism (67%) with large collections of atypical lymphocytes (55%), >20:1 CD4:CD8 ratio (79%), CD30 positivity (68%), angiocentricism (78%), folliculotropism (65%), granulomatous inflammation (14%), and follicular mucin (10%). A more refined understanding of clinical and histologic features in cutaneous ATLL may help clinicians and pathologists to more accurately diagnose patients with this uncommon disease, particularly in non-endemic areas.