

Journal Watch

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Topical 0.5% ivermectin lotion for treatment of head lice

Pariser D, Meinking TL, Bell M, Ryan W.
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This study evaluated the efficacy and safety of a topical formulation of ivermectin (0.5% lotion, Sklice, Sanofi Pasteur) compared with vehicle control, against head-lice infestation. Two multicentre, randomised, double-blinded parallel trials sponsored by industry were performed in the USA from March to July 2010. A total of 765 patients over six-months old with evidence of active infestation (defined by finding of three or more live lice on scalp or hair) and household members (with one or more live lice found) were recruited. They were given a tube of either topical ivermectin or vehicle to be applied to dry hair for 10 minutes before rinsing with water. Nit combing and other treatments were not allowed. The primary endpoint was the percentage of index patients in the intention-to-treat population who were louse-free one day after treatment and remained so after one and two weeks.

In both studies, the baseline characteristics in the intention-to-treat population were similar. The mean age was eight years. The majority of patients were female (77-85%) and white (over 95%) with a mean body weight of 31.6-31.8 kg. The combined intention-to-treat analysis showed that significantly more patients in the treatment group than vehicle-control group were louse-free one day (94.9% vs 31.3%, $p < 0.001$), one week (85.2% vs 20.8%, $p < 0.001$) and two weeks (73.8% vs 17.6%, $p < 0.001$) after treatment. Pruritus was significantly reduced as early as day two in treatment group compared to vehicle-control group (66.7% vs 42.6%, $p < 0.001$), which may be partially attributable to the emollient effect of the formulation. The frequency and severity of

adverse events (most commonly manifested as pruritus, excoriation and erythema) were similar in the treatment and vehicle-control groups (0.5-0.8% vs 1.2-1.5%).

In conclusion, a single, 10-minute, at-home topical application of 0.5% ivermectin was more effective than vehicle control in eliminating head-lice infestations of index case at one day, one week and two weeks after treatment. The efficacy was comparable to oral ivermectin at one day.

Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations

Flaherty K, Infante J, Daud A, Gonzalez R, Kefford R, Sosman J, et al.
N Engl J Med 2012;367:1694-703.

A phase 1 and 2 trial of combined treatment with selective BRAF inhibitor (dabrafenib) and selective MAPK kinase inhibitor (trametinib) was conducted to evaluate the pharmacokinetic activity, safety and clinical efficacy in prevention of melanoma progression. An open-label study involving 247 patients age 18 or above, with adequate organ function, and histologically confirmed metastatic melanoma with either BRAF V600E or V600K mutation were recruited. Patients with stable brain metastasis were allowed to enroll. They were randomly assigned to in 1:1:1 ratio to receiving combination therapy at low dose (dabrafenib 150 mg twice daily and trametinib 1 mg daily, abbreviated as 150/1), at full dose (dabrafenib 150 mg twice daily and trametinib 2 mg daily, abbreviated as 150/2), or dabrafenib monotherapy (150 mg twice daily). Treatment was continued until disease progression or death. The median duration of treatment was 6.1 and

11 months respectively in the monotherapy and combination (150/2) group.

There was no drug interaction between the two targeted therapies. Dose-limiting toxic effects at full dose (150/2), were infrequently observed, although recurrent neutrophilic panniculitis occurred which required dose reduction and treatment with systemic steroid. Cutaneous squamous-cell carcinoma was seen in 19% of patients receiving dabrafenib monotherapy; 7% in combination therapy (150/2), though the reduction was not significant ($p=0.09$). Pyrexia was more common in combination group (150/2) than in the monotherapy group (71% vs 26%). Other side-effects of MEK-inhibitors were more common in the combination group.

The median progression-free survival in the combination group (150/2) was 9.4 months compared with 5.8 months in monotherapy group (hazard ratio for progression or death 0.39, 95%CI 0.25-0.62, $p<0.001$). The rate of complete or partial response with combination 150/2 therapy was 76%, compared with 54% with monotherapy ($p=0.03$). One-year progression-free survival was 41% in the combination 150/2 group and 9% in the monotherapy group ($p<0.001$).

To conclude, full-dose combination therapy with dabrafenib and trametinib was safe and effective in prolonging progression-free survival in patients with V600-mutated metastatic melanoma. The most common adverse side effect was pyrexia. This combination treatment may be useful to combat the problem of BRAF resistance in melanoma.

A randomised, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis

Gottlieb AB, Langley RG, Strober BE, Papp KA, Klekotka P, Creamer K, et al.
Br J Dermatol 2012;167: 649-57.

This randomised double-blinded multicentre study was conducted between November 2009 and

December 2010 to assess the efficacy and safety of the addition of methotrexate to etanercept compared with etanercept monotherapy in moderate to severe psoriasis. All patients received etanercept 50 mg for 24 weeks were randomised 1:1 to oral methotrexate (combination group) or matching placebo (monotherapy group). The primary endpoint was PASI 75 at week 24. Secondary efficacy endpoints included PASI 75 at week 12, PASI 50 and PASI 90, static Physician's Global Assessment and BSA improvement at weeks 12 and 24. In total, 239 patients were enrolled in each arm with 211 in the combination group and 206 in the monotherapy group. Adverse effects (AEs) were the most common reasons to discontinue the study but only three serious AEs occurred in each group. At week 24, PASI 75 response was significantly higher for the combination group than the monotherapy group (77.3% vs. 60.3%; $P<0.0001$). Similar results occurred for PASI 50 at week 12 (combination: 92.4% vs. monotherapy: 83.8%; $P=0.01$) and week 24 (91.6% vs. 84.6%; $P=0.01$) and for PASI 90 at week 12 (34.0% vs. 23.1%; $P=0.03$) and week 24 (53.8% vs. 34.2%; $P=0.01$). There were significantly more patients treated with combination therapy than monotherapy with a static Physician's Global Assessment of clear / almost clear at week 12 (65.5% vs. 47.0%; $P=0.01$) and week 24 (71.8% vs. 54.3%; $P=0.01$). The authors thus concluded that the combination therapy with etanercept plus methotrexate had an acceptable tolerability and increased efficacy compared to etanercept monotherapy in patients with moderate to severe psoriasis.

Long-term neurological follow-up of HIV-positive patients diagnosed with syphilis

Muldoon EG, Mooka B, O'Dea S, Clarke S, Gourtney G, Lyons F, et al.
Int J STD AIDS 2012;23:676-8.

Syphilis and HIV are frequently co-infected and syphilis is known to facilitate the transmission of HIV. HIV infection can modulate syphilis manifestations and the serological response to therapy. HIV-infected syphilis patients have more severe forms of syphilis, persistency of cerebrospinal fluid (CSF) abnormalities and higher

serological failure rates. In addition, there were reports of relapse of neurosyphilis despite standard therapy. The aim of this study was to assess the long-term neurological outcome of HIV-infected patients co-infected with syphilis.

HIV-infected patients diagnosed to have syphilis received standard therapy prior to 2007 were identified. They were asked for consent to lumbar puncture and neurological examination. A total of 141 records of HIV-infected syphilis patients prior to 2007 were available: 51 patients were excluded because of death, lost to follow-up or transferred to other centres. In the remaining 90 patients, 45.5% (41/90) consented to have lumbar puncture and 87.8% (36/41) were successfully analysed. In these 36 patients, the mean age was 41-years-old. Most (74.3%) were men who have sex-with-men (MSM). The neurological examinations in all patients were normal except one patient who had had a serious head injury with long-term neurological deficit related to the injury. All CSF RPR were non-reactive. The mean CSF white cell count (WCC) was 1.41 cells/hpf and only one patient's CSF WCC (10.7 cells/hpf) was greater than normal (10 cells/hpf). The mean CSF protein was 36.45 mg/dL (ranged from 16-68 mg/dL) and ten patients' CSF proteins were greater than normal (40 mg/dL). All these were not significantly associated with CD4 counts, viral loads and the use of HAART therapy.

In conclusion, the findings were reassuring in that the HIV-infected patients who received standard syphilis therapy did not have long-term neurological consequences and that HIV-infected syphilis patients should be treated with the standard regimens as those who were not infected with HIV.

The outcome of treatment of early syphilis with different benzathine penicillin regimens in HIV-infected and -uninfected patients

Cousins DE, Taylor M, Lee V.

Int J STD AIDS 2012;23:632-4.

Most international guidelines like The British Association for Sexual Health and HIV (BASHH) and Centre for Disease Control of United States

(CDC US) recommend the same treatment for syphilis patients regardless of their HIV status. However, some authorities advocate two or three doses of benzathine penicillin in HIV-infected early syphilis patients and recent commentary has questioned the efficacy of single-dose benzathine penicillin in treatment for these patients. The aim of this study is to look at the outcome of treatment of early syphilis with different benzathine penicillin regimens in HIV-infected or non-infected patients.

During the first year of study (2006), the centre used the previous BASHH guidelines to treat HIV-infected early syphilis patient by two or three doses of benzathine penicillin. During the second year (2007), the centre followed the recent guidelines by using one dose of benzathine penicillin for both HIV-infected or uninfected patients. A total of 259 early syphilis patients were identified in 2006 and 2007. Overall 98.5% were men and 90.9% were men who have sex-with-men (MSM) and 30% were HIV-infected. About 75% (98/131) in 2006 cohort and 71% (91/128) in 2007 cohort were either RPR negative or sero-fast at 12 months. There were 12.4% and 3.8% of patients re-infected with syphilis in 2006 and 2007 cohort respectively.

For HIV-negative early syphilis patients, the cure rate in 2007 cohort was 80.5% compared with that in 2006, which was 67.1%. For HIV-infected patients, the cure rate was 64.1% in 2006 cohort and 78.9% in 2007 cohort. The differences were both not statistically significant.

In conclusion, single dose of benzathine penicillin for early syphilis treatment in either HIV-infected or non-infected patients does not affect the incidence of treatment failure.

Prognostic factors of paraneoplastic pemphigus

Leger S, Picard D, Ingen-Housz-Oro S, Arnault JP, Aubin F, Carsuzaa F, et al.

Arch Dermatol 2012;148:1165-72.

Paraneoplastic pemphigus (PNP) is a rare form of pemphigus usually associated with lymphoproliferative disorders and rarely associated with other malignant neoplasms. This is a retrospective study performed in 27

dermatology departments in France from 1992 to 2010 aim at studying the prognostic factors and survival in PNP.

A total 53 patients (31 males and 22 females) were identified for the study. The median age was 59 years and the associated neoplasms were chronic lymphocytic leukemia (n=16), non-Hodgkin's lymphoma (n=14), carcinoma (n=10), Castleman disease (n=5), thymoma (n=4) and some other lymphoproliferative diseases. Thirty-six patients (68%) had the neoplasm occurred before the PNP with a mean lapse time of 2.2 years. An associated neoplasm was found at the same time or after the occurrence of PNP in 8 and 9 patients respectively. There were mucosal lesions in 50 patients (94%) and five of them had only mucosal lesions without skin lesions. The mucosal area involved were mainly oral (n=47), conjunctival (n=28), genital (n=27), pharyngeal/laryngeal (n=12), esophageal (n=4) and bronchial (n=3). Pemphigus-like lesions were found in 48 patients (90%), erythema multiforme-like (EM-like) lesions were found in 10 patients (n=10) and other patients had lichen planus-like, pemphigoid-like or linear IgA dermatoses-like lesions. In the univariate analysis, the presence of EM-like lesions and keratinocyte necrosis were associated with decrease survival. In age and sex adjusted multivariate analysis, only the presence of EM-like lesions was associated with decrease survival (Hazard ratio 2.3, 95%CI 1.05-5.03, $p=0.037$). The sex and age were not associated with patients' prognosis, nor were the PNP antigens pattern and the initial severity of PNP associated with prognosis. The overall survival rate was 49% at 1 year, 41% at 3 years and 38% at 5 years. Totally 36 patients (68%) passed away in the study period.

This study shows that the prognosis of PNP is not as poor as previously reported, probably because of the inclusion of both severe and moderate cases. The presence of EM-like lesion was associated with reduced survival. The presence of necrotic keratinocyte when associated with severe disease initially and concomitant EM-like lesions were associated with poorer prognosis.

Expanding the psoriasis disease profile: interrogation of the skin and serum of patients with moderate to severe psoriasis

Suarez-Farinas M, Li K, Fuentes-Duculan J, Hayden K, Brodmerkel C, Krueger JG.

J Invest Dermatol 2012;132:2552-64.

This study aimed at determining more psoriasis-associated genes, which were differentially expressed in psoriatic lesions and may help finding a connection associated with metabolic diseases and cardiovascular risk. Furthermore, this study also compared the serum of psoriatic patients with healthy individuals to determine the overlap of differentially expressed genes and serum proteins.

Since 2001, a molecular approach to determine the pathophysiology of psoriasis was used in comparing the messenger RNA expression between psoriatic lesions and non-lesional skin of the same patient. Since then, research has been conducted to identify the cytokines and transcription factors controlling these altered gene expression into functional pathways. These disease pathways have been found to be associated with hundreds of psoriasis-associated genes (transcriptome).

Skin biopsy samples of lesional and non-lesional skin were obtained from 89 psoriatic patients. Blood samples for serum protein analysis were obtained from another 149 psoriatic patients and 162 healthy individuals. The psoriatic patients were not receiving active systemic treatment upon entering the study. Sixty-two psoriatic patients also gave serum samples for serum protein analysis. The average PASI of the psoriatic patients were 21 (± 10.2).

There were 4,175 differentially expressed genes identified in the psoriatic lesions defined by more than 2-fold change and a false recovery rate of <0.05 . This study also confirmed that many up-regulated genes were involved in various signaling pathways in the pathogenesis of psoriasis, such as interferon- γ , tumor necrosis factor, interleukin-17 signaling. There were also genes that were significantly important but previously not reported, such as renin, cytotoxic T-lymphocyte antigen (CTLA4) and Toll-like receptor (TLR3). The protein

products of these genes were also found at great levels in psoriatic lesions by immunohistochemical staining.

Twelve proteins were found to be significantly increased in the serum of psoriatic patients, ranging from 1.25 times to >3.5 times ($p=10^{-5}$ - 10^{-30}).

These proteins were mainly inflammatory cytokines or chemokines and were associated with corresponding elevated mRNA quantities in psoriatic lesions ($p<0.05$).

There have been two proposed explanations by which psoriasis leads to metabolic and cardiovascular diseases via its inflammatory mechanisms in the skin. Firstly, psoriatic lesions produce hormone-like proteins that affect cells of other systems (e.g. renin, vascular endothelial growth factor). Secondly, there is dysregulated gene expression in psoriatic lesions that may be governing the metabolic pathways associated with atherosclerosis, renin-angiotensin signaling, leptin signaling and others that is significant in comorbidities. The authors concluded that the additional psoriasis transcriptome and serum protein profiles found in this study offered further support for the inflammatory pathogenesis in psoriasis. In addition, the pathological changes in the skin of patients were highly suggestive of a relationship to systemic diseases and comorbidities such as cardiovascular and metabolic syndromes.

Oral glycopyrrolate as second-line treatment for primary paediatric hyperhidrosis

Paller AS, Shah PR, Silverio AM, Wagner A, Chamlin SL, Mancini AJ.
J Am Acad Dermatol 2012;67:918-23.

Primary focal hyperhidrosis is not uncommon among adolescents and children. It not only causes significant emotional and social distress, but also increases risk of cutaneous infection. First-line treatments include topical application of aluminum salts, but it can cause local irritation. Other

treatment modalities include botulinum toxin injection, ionopheresis and thoracic sympathectomy, but they are costly, painful and associated with surgical complications. Oral glycopyrrolate is an anti-cholinergic agents used in children for excessive salivation. The author aimed at assessing the efficacy and tolerability of oral glycopyrrolate in primary paediatric hyperhidrosis.

In this 10-year retrospective study, records of 159 paediatric patients with primary focal hyperhidrosis were reviewed. Thirty-one (19%) of them had excessive sweating on daily basis which led to major activities avoidance, and were prescribed at least one dose of oral glycopyrrolate. The dosage given ranged from 1 mg to 6 mg daily, in single or divided dose, according to the patients' response. Ninety percent of patients improved with treatment, of which 71% showed major improvement. Most patients claimed that the onset of action was quick, but short-lived. Oral glycopyrrolate was generally well-tolerated. Twenty-nine percent of them experienced some adverse effects, namely, dry eyes, dry mouth, blurring of vision and palpitations, which were dose-related. None of them required termination of the treatment due to side-effects.

The authors concluded that oral glycopyrrolate is a fast-acting, safe and effective treatment for those who failed topical aluminum chloride. However, this study was limited by its small sample size and retrospective study design.

Therapy with rituximab for autoimmune pemphigus: Results from a single-center observational study on 42 cases with long-term follow-up

Cianchini G, Lupi F, Masini C, Corona R, Puddu P, De Pita O.
J Am Acad Dermatol 2012;67:617-22.

Pemphigus is a chronic autoimmune blistering disease affecting the skin and mucous membranes. Mainstay of treatment includes systemic steroids together with steroid-sparing immunosuppressive agents. Rituximab had been shown to induce

significant improvement in patients with pemphigus vulgaris (PV) and pemphigus foliaceus (PF) in previous case reports or small case series. In this cohort study, the authors aimed at investigating the efficacy and tolerability of rituximab in management of PV and PF and its use in treating relapses.

A total of 42 patients with refractory pemphigus were recruited (37 with PV and 5 had PF). All of them were given two doses of rituximab 1000 mg-infusions 15 days apart initially. During rituximab infusion, oral prednisolone were given at 0.5 mg/kg and slowly tailed down, and all other immunosuppressive agents were stopped. An additional 500 mg rituximab infusion was given after 6 months if patients were partially or not responding to initial infusions. Afterwards, further 500 mg infusions were administered in case of relapses.

Thirty-six out of 42 patients achieved complete remission after initial infusions, while the remaining also achieved remission after an additional dose of rituximab 6 months afterwards. Among those who achieved remission after initial doses of rituximab, half of them remained in remission over a follow-up period of 12-59 months. While for the remaining, 6, 9 and 3 patients had one to three relapses respectively, which was controlled with one dose of 500 mg rituximab infusion.

No serious adverse effects that required hospitalisation and discontinuation of drugs occurred. Twelve patients had infusion reactions, 10 had infective complications and one developed parkinsonism one year after the last dose of rituximab.

The authors concluded that rituximab given together with steroid is effective in inducing remission in patients with pemphigus. Also, it can be used alone as maintenance in case of relapses. No major infections occurred and it was well-tolerated. However, this study was limited by the lack of control arm.

Toxic epidermal necrolysis: five years of treatment experience from a burn unit

Firoz BF, Henning JS, Zarzabal LA, Pollock BH. *J Am Acad Dermatol* 2012;76:630-5.

Toxic epidermal necrolysis (TENS) is a serious and life-threatening drug reaction. Previous studies showed conflicting results in whether active interventions alter mortality and the reliability of SCORTEN in predicting mortality.

In this cohort study, the authors summarised their experience in managing TENS patients in a single burn unit over a period of five years. A specific TENS protocol, which included nutritional support, careful fluid and electrolytes monitoring, wound care, and limited use of antibiotics, were adopted. IVIG 4 g/kg over 3 days was given to patients who were admitted to the unit within 72 hours of blistering. Otherwise, only supportive care were given. Cyclosporin was given to those who had limited surface area involvement, low SCORTEN score and were not contraindicated to cyclosporin.

A total of 82 TENS patients were enrolled and 29 died, which was accurately predicted by SCORTEN scoring on admission and at 48 hours. The four most common offending drugs in this cohort were trimethoprim/sulfamethazole (septrin), anticonvulsants, NSAIDs and allopurinol. Allopurinol carried the highest mortality among all these. The authors postulated that it might be due to the relatively long half-life of the active metabolites of allopurinol. Several factors were significantly associated with high mortality, which included older age, higher SCORTEN score, greater extent of body surface involvement, underlying medical comorbidities, and pre-existing metabolic syndrome and gout. Finally, IVIG did not alter the mortality rate in this cohort, despite the early initiation and high dose.

The authors concluded that SCORTEN could accurately predict the mortality in TENS patients, and the addition of pre-existing co-morbidities, metabolic syndrome and gout to the score further improved predictivity. However, the small sample size and the non-randomised study design limited the strength in assessing the efficacy of various treatment modalities.

A study on the epidemiology of rosacea in the U.K.

Spoendlin J, Voegel JJ, Jick SS, Meier CR.
Br J Dermatol 2012;167:598-605.

This large observational study was conducted between 1995 and 2009 to establish incidence rates (IRs) of diagnosed rosacea and the demographics of patients with rosacea in the United Kingdom (U.K.), to quantify the prevalence of ocular involvement and to explore various lifestyle risk factors of developing the disease. All rosacea patients in the U.K.-based General Practice Research Database were assessed during the study period and controls were matched 1:1 to case patients. Patients with rhinophyma or ocular rosacea only and less than three years of recorded history were excluded. In total, 60,042 rosacea cases and 60,042 controls were included. The overall IR of GP-diagnosed rosacea was 1.65 per 1000 person-years (py) (95% CI 1.63-1.66) with a higher IR in women (IR 1.92) than in men (IR 1.34), and peaked between the age of 40 and 59 years. Current smokers had a reduced relative risk of developing rosacea (OR 0.64, 95% CI 0.62-0.67). There were 12,480 (20.8%) rosacea cases found to have ocular symptoms, yielding the relative risk of 1.82 (95% CI 1.76-1.88). However, alcohol consumption was associated with only a marginal risk of increase for rosacea. The authors concluded that smoking was associated with a substantially reduced risk of developing rosacea and alcohol consumption did not play a major role in the pathophysiology of rosacea.

Delusional infestation and the specimen sign: a European multicentre study in 148 consecutive cases

Freudenmann RW, Lepping P, Huber M, Dieckmann S, Bauer-Dubau K, Ignatius R, et al.
Br J Dermatol 2012;167:247-51.

This retrospective cohort study was performed in six specialties institutions from four European countries between 2001 and 2007. All patients with suspected delusional infestation (DI) were included. Patient data regarding any true infestation, any self reported pathogen, whether the specimens were provided and how they were stored were analysed. All patients had a thorough clinical examination and all patient-provided specimens were studied microscopically. There were a total of 148 cases of DI and no medical evidence of a true infestation in any patient as evidenced by the examinations and laboratory tests performed. Only 35% believed themselves to be infested by parasites (52 of 148 cases) and 17% (25 of 148) believed themselves to be infested with an inanimate pathogen. Forty-eight per cent of the patients (71 of 148 cases) presented with specimens which were mostly skin particles or hair to prove their infestation and only 4% were stored in matchboxes (three of 71 patients with specimens). The authors thus suggested the use of 'delusional infestation' instead of 'delusional parasitosis' and the term 'the specimen sign' instead of 'the matchbox sign'.