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It's "possible that this is a syndrome: that eczema, ADHD, and sleeping problems are parts of one syndrome with another third or fourth underlying cause," said Dr. Jochen Schmitt.



COURTESY DR. JOCHEN SCHMITT

New Studies Show Atopy, ADHD Link

BY BRUCE JANCIN

BERLIN — Atopic dermatitis is strongly and independently associated with attention-deficit/hyperactivity disorder, three large German studies suggest.

If the relationship is causal—and that's an unsettled issue—then atopic dermatitis would explain roughly 10% of all cases of ADHD, Dr. Jochen Schmitt estimated at the annual congress of the European Academy of Dermatology and Venereology.

Atopic dermatitis is the most common chronic inflammatory disorder in childhood, and ADHD is the most common psychiatric diagnosis. The nature of the relationship is a classic chicken-versus-egg question, he said.

"As dermatologists, we first think that eczema causes sleeping problems, and this then would maybe cause ADHD. But a close friend of mine who is a psychiatrist says, no, ADHD causes psychologic distress and this distress is an exacerbating

factor for eczema," explained Dr. Schmitt, a dermatologist at Carl Gustav Carus Technical University in Dresden, Germany.

"It's also possible that this is a syndrome: that eczema, ADHD, and sleeping problems are parts of one syndrome with another third or fourth underlying cause. And it's even possible that all these things are true: that eczema triggers ADHD and vice versa and that sleeping problems could play a crucial role," he continued.

Dr. Schmitt first became interested in the relationship between atopic dermatitis and ADHD after learning of a Dutch group's hypothesis that some cases of ADHD are an allergic hypersensitivity disorder (Pediatr. Allergy Immunol. 2009;20:107-12).

Dr. Schmitt and his coinvestigators reviewed a German administrative health care database containing complete information on the outpatient care of 600,000 residents of Saxony. They identified 1,436 subjects

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INSIDE

Oral Exterminator

Ivermectin beats topical for treating head lice patients.

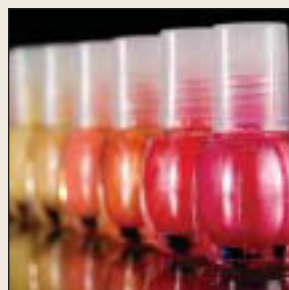
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Vitiligo study finds 87% graft survival rate.

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Color Me Rashy

A skin rash-causing nail polish and other 'organic' products explored.

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Red Flags Rule Delayed Again

Compliance aimed at preventing identity theft postponed until June.

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Drop Methotrexate At Week 12 in Poor Responders

Less than PASI-50 flags need for a biologic.

BY BRUCE JANCIN

BERLIN — Psoriasis patients who show less than a PASI-50 response to 20 mg/wk of methotrexate by week 12 are unlikely to benefit from dosage increases or longer therapy, according to a new analysis of the CHAMPION study.

Week 12 has been found to be a useful decision point for discontinuing methotrexate and moving on to a biologic agent, said Dr. Jean-Hilaire Saurat, professor of dermatology at the University of Geneva.

"With the data we've obtained with CHAMPION, our understanding of how the treatment should be conducted

should be reconsidered. We know that probably by week 12 we should know if the patient will respond or not," said Dr. Saurat.

CHAMPION (Comparative Study of Adalimumab vs. Methotrexate vs. Placebo in Patients With Psoriasis) was a phase III, 16-week, double-blind, randomized trial in patients with moderate to severe psoriasis (Br. J. Dermatol. 2008;158:558-66).

The study provides the only existent placebo-controlled methotrexate data, noted Dr. Suarat, who presented the post hoc subanalysis results at the annual congress of the Euro-

See **Methotrexate** page 4

CASE OF THE MONTH



COURTESY DR. BENJAMIN EHST

A healthy 31-year-old woman from eastern Oregon presented with a 3- to 4-month history of multiple, new, asymptomatic "moles" over her buttocks, thighs, and lower torso. Besides delivering a baby 10 months prior, her past medical history and review of systems was noncontributory except for gestational diabetes that was controlled at the time with metformin. What's your diagnosis? See **Case of the Month**, page 43.

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Cutoff Point Defined by Study

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pean Academy of Dermatology and Venereology.

CHAMPION included 103 evaluable patients randomized to 7.5 mg of oral methotrexate once weekly for 2 weeks, 10 mg weekly for the next 2 weeks, and then 15 mg/wk for 4 weeks.

The 40 patients with at least a PASI-50 response after 8 weeks—that is, a 50% reduction from baseline in Psoriasis Area and Severity Index scores—were deemed

early responders. They remained on methotrexate 15 mg/wk for the rest of the 16-week study.

Patients with less than a PASI-50 at week 8 had their dosage increased to 20 mg/wk for 4 weeks. If at week 12 they had achieved a PASI-50 response they stayed on 20 mg/wk for the final 4 weeks of the study; if not, their dosage was increased to 25 mg/wk.

The 22 participants who reached PASI-

50 after 8 weeks at dosages greater than 15 mg were classified as late responders; the 41 who never attained PASI-50 were deemed late nonresponders.

The mean weekly methotrexate dosage at 16 weeks was 14.5 mg in early responders, 19.5 mg in late responders, and 23.2 mg in late nonresponders. After 16 weeks, 27% of subjects had a PASI-75 response on a maximum dose of 15 mg/wk.

“The good news is in the responders the response to methotrexate is as good as to a biologic like adalimumab [Humira]. There is a group of patients on

methotrexate who are extremely happy, and you do not need high doses to reach this response,” Dr. Saurat said.

The new findings from CHAMPION will be particularly useful for European physicians because psoriasis patients who require systemic therapy have to be treated with methotrexate before biologics can be considered, he suggested.

Audience member Dr. Craig L. Leonardi pointed out that methotrexate is still widely prescribed in the United States as well.

“I use methotrexate a lot these days. I’ve got hundreds of patients on it. ... There’s clearly a group of patients who do very well with this drug at low doses. It would be spectacular if we could



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Brief Summary

Retin-A Micro® (tretinoin gel) microsphere, 0.1% and 0.04% is a formulation containing 0.1% or 0.04%, by weight, tretinoin for topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate/glycol dimethacrylate crosspolymer porous microspheres (MICROSPONGE® System) to enable inclusion of the active ingredient, tretinoin, in an aqueous gel.

IMPORTANT NOTE: This information is a BRIEF SUMMARY of the complete prescribing information provided with the product and therefore should not be used as the basis for prescribing the product. This summary has been prepared by deleting information from the complete prescribing information such as certain text, tables, and references. The physician should be thoroughly familiar with the complete prescribing information before prescribing the product.

INDICATIONS AND USAGE: Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, is indicated for topical application in the treatment of acne vulgaris. The safety and efficacy of the use of this product in the treatment of other disorders have not been established.

CONTRAINDICATIONS: This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted.

PRECAUTIONS:

General:

- The skin of certain individuals may become excessively dry, red, swollen, or blistered. If the degree of irritation warrants, patients should be directed to temporarily reduce the amount or frequency of application of the medication, discontinue use temporarily, or discontinue use all together. Efficacy at reduced frequencies of application has not been established. If a reaction suggesting sensitivity occurs, use of the medication should be discontinued. Excessive skin dryness may also be experienced; if so, use of an appropriate emollient during the day may be helpful.
- Unprotected exposure to sunlight, including sunlamps, should be minimized during the use of Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. Use of sunscreen products (SPF 15) and protective clothing over treated areas are recommended when exposure cannot be avoided.
- Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.
- Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, should be kept away from the eyes, the mouth, paranasal creases of the nose, and mucous membranes.
- Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.

Information for Patients: A Patient Information Leaflet has been prepared and is included with each package of Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%.

Drug Interactions: Concomitant topical medication, medicated or abrasive soaps and cleansers, products that have a strong drying effect, products with high concentrations of alcohol, astringents, or spices should be used with caution because of possible interaction with tretinoin. Avoid contact with the peel of limes. Particular caution should be exercised with the concomitant use of topical over-the-counter acne preparations containing benzoyl peroxide, sulfur, resorcinol, or salicylic acid with Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%. It also is advisable to allow the effects of such preparations to subside before use of Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, is begun.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 91-week dermal study in which CD-1 mice were administered 0.017% and 0.035% formulations of tretinoin, cutaneous squamous cell carcinomas and papillomas in the treatment area were observed in some female mice. These concentrations are near the tretinoin concentration of these clinical formulations (0.04% and 0.1%). A dose-related incidence of liver tumors in male mice was observed at those same doses. The maximum systemic doses associated with the administered 0.017% and 0.035% formulations are 0.5 and 1.0 mg/kg/day, respectively. These doses are two and four times the maximum human systemic dose applied topically, when normalized for total body surface area. The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose (MTD) of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice. There was no evidence of carcinogenic potential when 0.025 mg/kg/day of tretinoin was administered topically to mice (0.1 times the maximum human systemic dose, normalized for total body surface area). For purposes of comparisons of the animal exposure to systemic human exposure, the maximum human systemic dose applied topically is defined as 1 gram of Retin-A Micro (tretinoin gel) microsphere, 0.1% applied daily to a 50 kg person (0.02 mg tretinoin/kg body weight).

Dermal carcinogenicity testing has not been performed with Retin-A Micro (tretinoin gel) microsphere, 0.04% or 0.1%.

Studies in hairless albino mice suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect has been confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources.

The mutagenic potential of tretinoin was evaluated in the Ames assay and in the *in vivo* mouse micronucleus assay, both of which were negative.

The components of the microspheres have shown potential for genetic toxicity and teratogenesis. EGDMA, a component of the excipient acrylates copolymer, was positive for induction of structural chromosomal aberrations in the *in vitro* chromosomal aberration assay in mammalian cells in the absence of metabolic activation, and negative for genetic toxicity in the Ames assay, the HGPRT forward mutation assay, and the mouse micronucleus assay.

In dermal Segment I fertility studies of another tretinoin formulation in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (4 times the maximum human systemic dose applied topically, and normalized for total body surface area), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day (2 times the maximum human systemic dose applied topically and normalized for total body surface area) and above were observed. In oral Segment I and Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (17 times the human topical dose normalized for total body surface area).

Dermal fertility and perinatal development studies with Retin-A Micro (tretinoin gel) microsphere, 0.1% or 0.04%, have not been performed in any species.

Pregnancy: Teratogenic Effects: Pregnancy Category C.

In a study of pregnant rats treated with topical application of Retin-A Micro (tretinoin gel) microsphere, 0.1%, at doses of 0.5 to 1 mg/kg/day on gestation days 6-15 (4 to 8 times the maximum human systemic dose of tretinoin normalized for total body surface area after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%) some alterations were seen in vertebrae and ribs of offspring. In another study, pregnant

New Zealand white rabbits were treated with Retin-A Micro (tretinoin gel) microsphere, 0.1%, at doses of 0.2, 0.5, and 1.0 mg/kg/day, administered topically for 24 hours a day while wearing Elizabethan collars to prevent ingestion of the drug. There appeared to be increased incidences of certain alterations, including domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species, at 0.5 and 1.0 mg/kg/day. Similar malformations were not observed at 0.2 mg/kg/day, 3 times the maximum human systemic dose of tretinoin after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area. In a repeat study of the highest topical dose (1.0 mg/kg/day) in pregnant rabbits, these effects were not seen, but a few alterations that may be associated with tretinoin exposure were seen. Other pregnant rabbits exposed topically for six hours to 0.5 or 0.1 mg/kg/day tretinoin while restrained in stocks to prevent ingestion, did not show any teratogenic effects at doses up to 17 times (1.0 mg/kg/day) the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, adjusted for total body surface area, but fetal resorptions were increased at 0.5 mg/kg. In addition, topical tretinoin in non Retin-A Micro (tretinoin gel) microsphere formulations was not teratogenic in rats and rabbits when given in doses of 42 and 27 times the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area, respectively, (assuming a 50 kg adult applied a daily dose of 1.0 g of 0.1% gel topically). At these topical doses, however, delayed ossification of several bones occurred in rabbits. In rats, a dose-dependent increase of supernumerary ribs was observed.

Oral tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters, and subhuman primates. Tretinoin was teratogenic in Wistar rats when given orally or topically in doses greater than 1 mg/kg/day (8 times the maximum human systemic dose normalized for total body surface area). However, variations in teratogenic doses among various strains of rats have been reported. In the cynomolgus monkey, which metabolically is more similar to humans than other species in its handling of tretinoin, fetal malformations were reported for doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (83 times the maximum human systemic dose normalized for total body surface area), although increased skeletal variations were observed at all doses. Dose-related increases in embryolethality and abortion also were reported. Similar results have also been reported in pigtail macaques.

Topical tretinoin in animal teratogenicity tests has generated equivocal results. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (8 times the maximum human systemic dose normalized for total body surface area). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day was topically applied. Supernumerary ribs have been a consistent finding in rats when dams were treated topically or orally with retinoids.

There are no adequate and well-controlled studies in pregnant women. Retin-A Micro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty human cases of temporally associated congenital malformations have been reported during two decades of clinical use of Retin-A. Although no definite pattern of teratogenicity and no causal association has been established from these cases, five of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

Non-Teratogenic Effects: Topical tretinoin has been shown to be fetotoxic in rabbits when administered 0.5 mg/kg/day (8 times the maximum human systemic dose applied topically and normalized for total body surface area), resulting in fetal resorptions and variations in ossification. Oral tretinoin has been shown to be fetotoxic, resulting in skeletal variations and increased intrauterine death in rats when administered 2.5 mg/kg/day (21 times the maximum human systemic dose applied topically and normalized for total body surface area).

There are, however, no adequate and well-controlled studies in pregnant women.

Animal Toxicity Studies: In male mice treated topically with Retin-A Micro (tretinoin gel) microsphere 0.1%, at 0.5, 2.0, or 5.0 mg/kg/day tretinoin (2, 8, or 21 times the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area) for 90 days, a reduction in testicular weight, but with no pathological changes were observed at the two highest doses. Similarly, in female mice there was a reduction in ovarian weights, but without any underlying pathological changes, at 5.0 mg/kg/day (21 times the maximum human dose). In this study there was a dose-related increase in the plasma concentration of tretinoin 4 hours after the first dose. A separate toxicokinetic study in mice indicates that systemic exposure is greater after topical application to unrestrained animals than to restrained animals, suggesting that the systemic toxicity observed is probably related to ingestion. Male and female dogs treated with Retin-A Micro (tretinoin gel) microsphere, 0.1%, at 0.2, 0.5, or 1.0 mg/kg/day tretinoin (5, 12, or 25 times the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area, respectively) for 90 days showed no evidence of reduced testicular or ovarian weights or pathological changes.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Retin-A Micro (tretinoin gel) microsphere, 0.1% or 0.04%, is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

Geriatric Use: Safety and effectiveness in a geriatric population have not been established. Clinical studies of Retin-A Micro did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS:

The skin of certain sensitive individuals may become excessively red, edematous, blistered, or crusted. If these effects occur, the medication should either be discontinued until the integrity of the skin is restored, or the medication should be adjusted to a level the patient can tolerate. However, efficacy has not been established for lower dosing frequencies.

True contact allergy to topical tretinoin is rarely encountered. Temporary hyper- or hypopigmentation has been reported with repeated application of tretinoin. Some individuals have been reported to have heightened susceptibility to sunlight while under treatment with tretinoin.

OVERDOSAGE: Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, is intended for topical use only. If medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. Oral ingestion of large amounts of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

Rx only.

Patent Nos.: 4,690,825; 5,145,675 & 5,955,109

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‘The good news is in the responders the response to methotrexate is as good as to a biologic like adalimumab.’

DR. SAURAT

predict which ones,” said Dr. Leonardi of the department of dermatology at Saint Louis University.

Unfortunately, Dr. Saurat said, no baseline predictors of early response in CHAMPION could be identified. Of note, however, patients destined for ear-



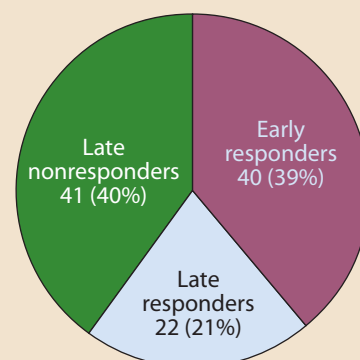
‘There’s clearly a group of patients who do very well with this drug [methotrexate] at low doses.’

DR. LEONARDI

ly responder status at week 8 already had a mean 40% reduction in PASI scores after just 4 weeks on methotrexate at 15 mg/wk.

The CHAMPION trial was sponsored by Abbott, which manufactures adalimumab. Dr. Saurat is an adviser to the company. Dr. Leonardi has served as a consultant to manufacturers of biologic agents for psoriasis. ■

Patient Response to Methotrexate



Note: Early response = PASI-50 at 8 weeks; late response = PASI-50 after 8 weeks; nonresponse = no PASI-50.
Source: Dr. Saurat