

area (the same geographic catchment area as the TCH Allergy and Immunology Clinic) is 5.0%, with a rate of 6.3% reported for all of Texas.⁸ Compared to these studies, we observed a several-fold higher prevalence of asthma in our patients with HIV. This higher prevalence of asthma diagnoses and asthma medication use may suggest that children and young adults with HIV infection on the improved antiretroviral drug regimens currently available are at increased risk for developing asthma due to immune preservation or reconstitution.

There was evidence that antiretroviral medications preserved CD4⁺ T-cell numbers prior to the development of asthma, because most pediatric patients perinatally infected with HIV in the United States, including our cohort, are treated from birth. As this group of patients with HIV overall has relatively well-controlled disease, with only 6 meeting immunologic criteria for AIDS, it may not be the ideal population in which to correlate CD4⁺ T-lymphocyte levels with asthma, although a few showed immune reconstitution prior to requiring asthma medications. There was a suggestion of a treatment effect in the subjects with asthma in that they had lower CD8⁺ T-cell counts and percentages. A prospective study of individuals with HIV (study in progress) is needed to determine whether or not there is a link between immune preservation or reconstitution due to improved HIV therapy and the development of asthma.

Our study speaks to the activation of CD4⁺ T lymphocytes confronting infectious agents (HIV in this case) with release of inflammatory cytokines as a possible explanation of the increased prevalence of asthma in the general population.⁹ These findings indicate a need for additional research to determine whether or not the immune preservation or restoration observed with treatment of HIV infection promotes airway inflammation and hyperreactivity that may necessitate initiation of or changes in asthma medications. More careful screening for asthma in children and young adults with HIV may also be appropriate, as more aggressive asthma management may decrease the need for potentially immunosuppressive asthma medications in an immunocompromised population already at risk.

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Successful treatment of delayed pressure urticaria with anti-TNF- α

To the Editor:

A 42-year-old white male presented for treatment of psoriasis that had begun 17 years ago and was overwhelming him. The patient's skin was affected with severe erythrodermia; the Psoriasis Area and Severity Index (PASI) was 18.3. On inquiry, the patient reported that he also had delayed pressure urticaria (DPU) for 14 years. If pressure was applied anywhere to the skin, the patient would experience swelling, burning, itching, and wheals 4 to 6 hours later at the pressure site. The symptoms would spontaneously resolve completely 10 to 14 hours later. The patient did not have arthritis, and he did not experience spontaneous wheals without a pressure stimulus. The general physical assessment showed that the patient was otherwise in good general health and was coping well. There was no known DPU in the family history; his father had had psoriasis. The results of laboratory tests were normal (tryptase 8.83 μ g/L [<17 μ g/L], angiotensin converting enzyme 24.0 [range 15-80 U/L], erythrocyte sedimentation rate 12/25).

DPU is a distinct entity, the time course of which differentiates it from other conditions. The time course of this patient's symptoms made it clear that he had DPU. After the first year of suffering symptoms, the patient was

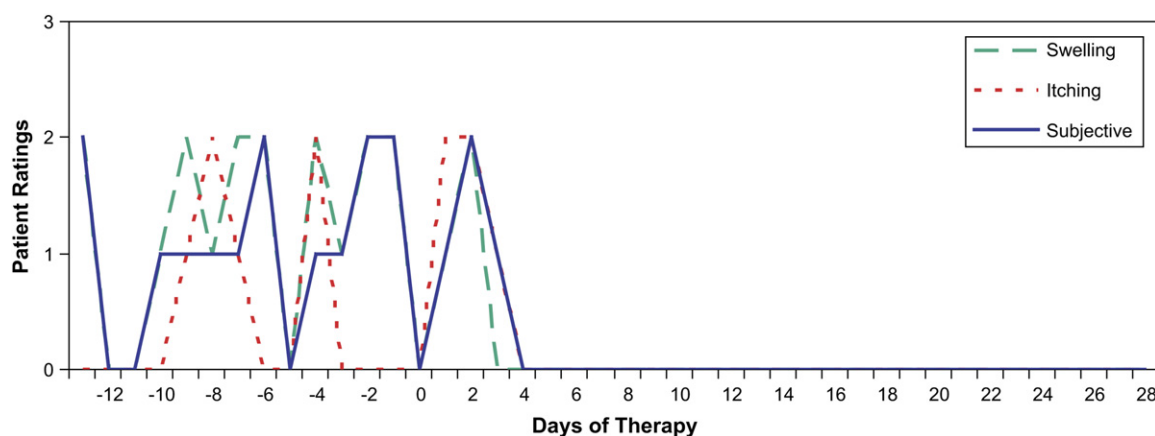


FIG 1. Patient diary of symptoms. Symptoms were rated on a 4-point scale from 0 to 3. The days of therapy on the x-axis indicate how many days of etanercept therapy had elapsed. Day 0 designates the day therapy with etanercept was started. The negative days indicate the number of days pretreatment. The x-axis ends after 28 days of therapy for sake of space, but no further symptoms were recorded for the remaining time of the clinical diary. Etanercept was taken on days 3, 7, 10, 14, 17, 21, 24, and 28. Cetirizine (10 mg) was taken on days -14, -6, -2, -1, and 2.

diagnosed with DPU and prescribed 20 mg cetirizine daily, which was reduced to 10 mg daily after 8 years. After many years of cetirizine and avoiding pressure, the symptoms were stable at a low level but increased again if cetirizine was discontinued. Up until the time of presentation, the patient was taking 10 mg cetirizine daily (plus an additional 10 mg/day when needed) to minimize his DPU symptoms, and he was using local care products and greasing creams for his psoriasis. To prevent pressure-induced symptoms, the patient avoided belts and close-fitting trousers and wore shoes that were wide and soft. He could not ride a bicycle, and he had to sit on a pillow at concerts.

No known cure has been reported for DPU, and a long list of past treatments had failed to make any tolerable improvement in either of this patient's conditions: local glucocorticoids, local dithranol, repeated psoralen + ultraviolet (UV) A irradiation including systemically repeated UVB, repeated balneotherapy, methotrexate, fumaric acid, isotretinoin, neotigason (acitretin), and cyclosporin A. The patient had been able to significantly reduce his DPU severity by long-term use of cetirizine and behavioral prevention. Nonetheless, a mild level of DPU remained, and the patient was overwhelmed by psoriasis.

It has often been written that the pathogenesis of DPU is not well understood and treatment remains unsatisfactory.^{1,2} But enough is known to begin finding better treatment strategies. It has been shown that TNF- α exists in patients with DPU at significantly elevated levels in many types of cells, including lesional and nonlesional endothelial cells from the upper and lower dermis, perivascular cells of lesional and nonlesional upper dermis specimens, and lesional and nonlesional epidermis specimens, among others.³ TNF- α upregulates E-selectin,⁴ an adhesion molecule that is found in significantly elevated levels during the symptomatic phase of DPU.⁵ E-selectin

is the primary mediator of neutrophil adherence⁴ and is involved in the adherence of eosinophils.⁶ In its symptomatic phase, DPU involves mast cell activation and a deep dermal infiltrate of neutrophils and eosinophils.^{1,5,7}

It is thought that eosinophils play a pivotal role in the manifestation of DPU.² In sum, the application of pressure is a physical stimulus that reaches down into the lower dermis, setting off an upregulation of TNF- α (and other mediators) that then leads to an infiltrate of eosinophils (and other cells) in the lower dermis, which creates DPU's characteristic erythematous deep-seated swellings. Based on these available scientific findings, it would have been reasonable to suspect that TNF- α might have been playing a key role in this patient's DPU and that inhibiting TNF- α might improve it.

Etanercept is a recently developed competitive inhibitor of the proinflammatory cytokine TNF- α . It binds with TNF- α at a high affinity, thus preventing TNF- α from binding to its cell surface receptors.^{8,9} In clinical trials, etanercept has been shown to be effective against psoriasis, without notable side effects,⁸ as well as in rheumatoid diseases.⁹

Etanercept was started at the recommended dose of 25 mg subcutaneously twice per week after contraindications were ruled out. For 13 days before therapy and for 63 days during therapy, the patient kept a diary documenting his urticarial activity by recording daily the number of swellings and assessing the intensity of itching/burning (0 = none, 1 = mild, 2 = moderate, 3 = extreme). The diary also included a scale for the assessment of subjective complaints (0 = none, 1 = mild, 2 = moderate, 3 = extreme) and a record of cetirizine intake. During the 13-day period between his initial presentation and the start of therapy with etanercept, the patient's cetirizine prescription was reduced to an "as needed" basis, as a quasi-without period.

During the 13 days of baseline before starting etanercept, the patient's clinical diary reported a daily average of 1.3 swellings, an average itching/burning intensity of 0.5, a subjective complaint rating of 1.1, and 4 days when 10 mg cetirizine was taken. Two days after the first dosage of etanercept, the final dosage of cetirizine was taken. By the fifth day of the therapy period (that is, the fourth day after the day of administering the first dose of etanercept and 1 day after the second dose), all 4 of these measures had dropped to zero, and they all remained at zero every day through the end of the clinical diary (62 days after administration of the first dose) (Fig 1). The patient did not report any side effects.

The psoriasis was improved after 4 weeks of therapy, but lesions persisted, so the dosage was increased to 50 mg subcutaneously twice per week starting on the 54th day of therapy. This led to a further but only temporary improvement of the psoriasis, so 5 months after starting etanercept, it was replaced with infliximab. Infliximab, another TNF- α inhibitor, has been used as recommended since that time, for over 8 months. At the last follow-up, 1 year after the disappearance of all DPU symptoms, the patient was still free of any DPU symptoms and the PASI has remained at less than 7. The patient is now able to wear any kind of clothing (including belts, normal trousers, and hard shoes). He is able to ride a bicycle and sit at concerts without a pillow.

This is the first report of successful treatment of DPU with a TNF- α inhibitor. The rapid and complete improvement supports the purported pathogenic role of TNF- α in DPU. Further clinical trials should investigate whether this benefit is generalizable to other patients with DPU. Coordinating clinical cases with biopsy studies would help to illuminate the biochemical mechanisms and cellular effects of etanercept in DPU. This case shows that DPU can be rapidly and successfully treated with etanercept at the recommended dosage without side effects.

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