doi:10.36849/JDD.2020.2106

Tumor Necrosis Factor Inhibitor-Induced Psoriasis in a Pediatric Crohn's Disease Patient Successfully Treated with Ustekinumab

Lauren Bonomo MD,[a] Ellen H. de Moll MD,[b] Linden Li,[b] Lauren Geller MD,[b] Michael I. Gordon DO,[c] David Dunkin MD[d]

[a]Icahn School of Medicine at Mount Sinai, New York, NY
[b]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY
[c]Nova Southeastern University College of Osteopathic Medicine, Davie, FL
[d]Department of Pediatric Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY

ABSTRACT

Background: Tumor necrosis factor (TNF) inhibitors are widely used in pediatric patients with inflammatory bowel disease, as well as psoriasis. However, there is growing evidence that these medications can also paradoxically induce a psoriasiform skin reaction in a subset of patients.
Goals: We seek to share our experience in treating severe TNF inhibitor-induced psoriasis in a pediatric patient with Crohn's disease.
Study: We report a case of a 10-year-old female with Crohn's disease, who developed psoriasis after twelve months of infliximab therapy. Her skin disease was recalcitrant to topical therapies, methotrexate, and phototherapy.
Results: The patient was transitioned to ustekinumab with significant improvement in her symptoms and maintenance of remission of her bowel disease.
Conclusion: This is the first reported case of a school-age pediatric patient with TNF inhibitor-induced psoriasis treated with ustekinumab. Controlled trials are warranted to fully assess the safety and efficacy of ustekinumab for treating TNF inhibitor-induced psoriasis in the pediatric population.

J Drugs Dermatol. 2020;19(3):328-331. doi:10.36849/JDD.2020.2106

INTRODUCTION

Case Synopsis: A 10-year-old female with a history of Crohn's disease (CD) presented with a rash on her scalp and trunk and associated hair loss for several months. She had tried over the counter salicylic acid shampoo, ketoconazole shampoo, and topical corticosteroids without improvement. The rash was painful and she had begun to have hair loss as well. She was diagnosed with Crohn's disease at the age of 6 when she presented with abdominal pain and erythema nodosum bilaterally on her shins. She developed watery diarrhea, fevers, and weight loss soon after that. She was initially treated with prednisone as a bridge to mercaptopurine. She was well until a year later when she had elevated liver function tests and pancytopenia likely due to mercaptopurine. She was then switched to infliximab with good control of her gastrointestinal symptoms, normalization of her labs and mucosal healing on endoscopies. She was well for twelve months prior to the development of any rashes. Family history was negative for psoriasis but positive for a father with Crohn's disease.

On physical exam, she had erythematous scaly plaques on the scalp, upper chest, and back. She also had patches of alopecia on her posterior scalp. The clinical findings were consistent with psoriasis, and given her history, it was thought to be most likely tumor necrosis factor (TNF) antagonist-induced. She was started on fluocinonide 0.05% solution for the scalp and triamcinolone 0.025% ointment for the trunk twice daily for two weeks. After two weeks, minimal improvement was noted with these topical medications so weekly oral methotrexate was added to her regimen. However, after four weeks of methotrexate, the patient's skin disease had worsened, with new psoriatic plaques of the face, ears, neck, trunk, and bilateral upper and lower extremities and worsening alopecia (Figure 1). The decision was then made to transition her from infliximab to ustekinumab, with the goal of simultaneously treating both her Crohn's disease and psoriasis. While awaiting insurance approval for ustekinumab she also started narrowband ultraviolet (NBUVB) phototherapy.

The patient received an induction dose of ustekinumab 260 mg IV and then transitioned to a maintenance dose of ustekinumab 90 mg subcutaneously every 8 weeks while continuing methotrexate 10mg orally once a week and NBUVB phototherapy twice weekly. Within 8 weeks, the psoriatic plaques on her trunk and extremities had almost completely resolved with a

FIGURE 1. Patient with psoriatic plaques of the face, ears, neck, trunk and bilateral upper and lower extremities and worsening alopecia, on fluocinonide 0.05% solution, triamcinolone 0.1% ointment, and methotrexate.

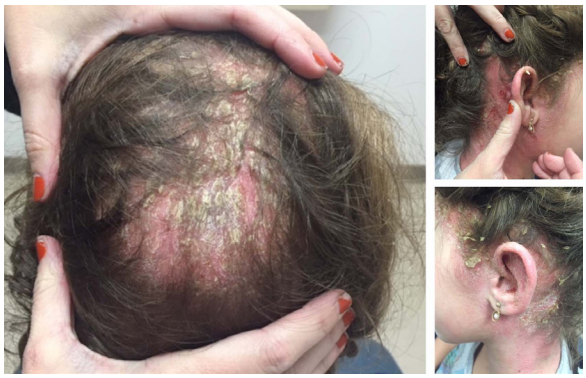
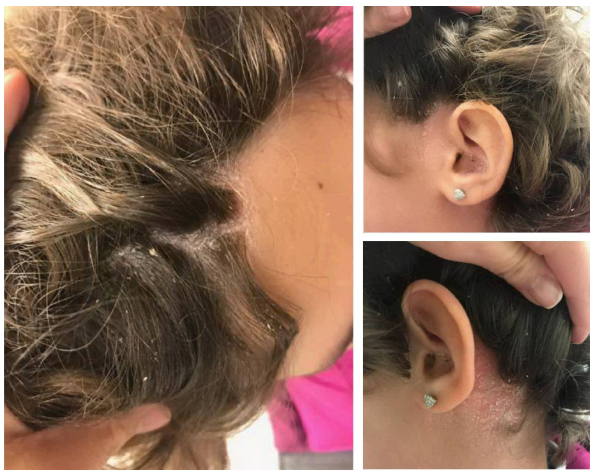


FIGURE 3. After treatment with ustekinumab and topical corticosteroids, patient has minimal scaly plaques of the scalp, with complete hair regrowth.



few patches remaining on her elbows and umbilicus. The psoriatic plaques on her scalp had improved as well, and she noted regrowth of her hair. Methotrexate and phototherapy were then discontinued. One year later, the patient continued to do well. Her Crohn's disease remained asymptomatic with complete mucosal healing throughout her gastrointestinal tract, as demonstrated by endoscopy and colonoscopy (Figure 2). She continued to have mild erythematous scaly patches on the scalp and ears, however these areas were under better control with topical corticosteroids, and her hair had completely regrown (Figure 3). In the hope of further improving her psoriasis, her dose interval of ustekinumab was then shortened to every 6 weeks and the skin patches completely cleared without any other medications (Figure 4). She has not had any adverse effects from the ustekinumab.

FIGURE 2. Colonoscopy photos from the initial diagnosis (diagnostic) and from after treatment with ustekinumab (post-ustekinumab) showing the rectum and left colon. The initial colonoscopy at diagnosis revealed patchy inflammation and ulceration throughout the colon similar to those shown here. The ileum was not intubated on this scope. The colonoscopy after treatment with ustekinumab showed completely normal mucosa in the entire colon and terminal ileum.

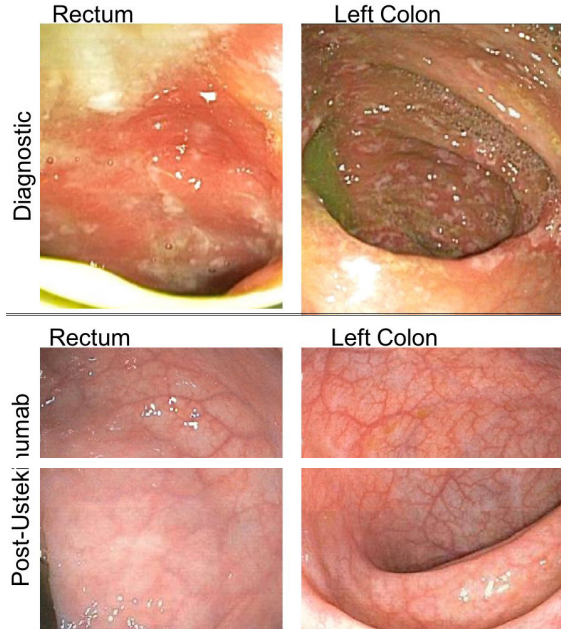
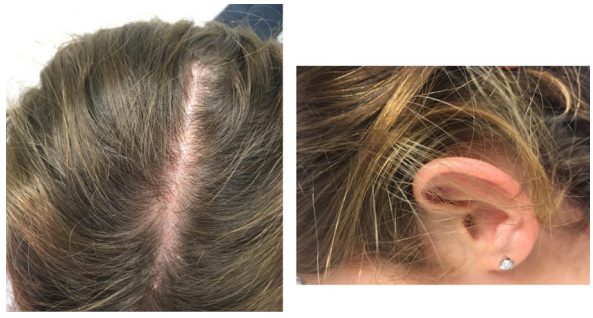


FIGURE 4. After dose interval of ustekinumab was shortened to every 6 weeks, without use of topical corticosteroids. Skin patches have completely resolved.



CASE DISCUSSION

TNF inhibitors are used for several pediatric conditions, including Crohn's disease and ulcerative colitis. Psoriasiform skin lesions are a well-documented side effect in up to 5% of patients.[1] There are currently five approved TNF inhibitors in the United States: etanercept, infliximab, adalimumab, golimumab, and certolizumab, and all have been associated with this side effect. The mean time to development is 10-17 months, although this is highly variable and has been reported years after initiation of therapy as well.[2-4] Sites most commonly affected include

the palms, soles, and scalp, with secondary alopecia, although guttate and plaque psoriasis are also described.[1-3,5] Smoking and female sex have been proposed as risk factors.[1,6]

Treatment of infliximab-induced psoriasis should follow a similar treatment ladder as traditional psoriasis, starting with topical therapy. In one study by Malkonen et al, of 84 children with inflammatory bowel disease who developed infliximab-induced psoriasis, most responded well to topical corticosteroids, with only 7 patients requiring discontinuation of infliximab, and none requiring phototherapy or systemic therapy.[7] Similar results were seen by Guerra et al., with 78% responding to topical corticosteroids.[6] However, Ko et al examined 127 cases of TNF-induced psoriasis and found topical corticosteroids led to resolution in only 25%.[2] In cases unresponsive to topical corticosteroids, systemic therapies such as cyclosporine or methotrexate can be added. In more severe or recalcitrant cases, both discontinuation of the TNF inhibitor and systemic therapy may be required.[2] In the Ko et al series, TNF inhibitor discontinuation and initiation of systemic therapy was most effective, leading to resolution of symptoms in 64% of cases. Switching within the anti-TNF family of medications appears to be ineffective, with resolution of 0 to 15% in different case series, indicating a likely class effect.[2,3]

Ustekinumab is a monoclonal antibody that binds to the p40 subunit of the interleukin 12 and 23 cytokines. It has shown remarkable efficacy in adult psoriasis and was recently approved in October 2017 by the Food and Drug Administration for moderate to severe psoriasis in adolescents aged 12 and older.[8] There are a few case reports and case series demonstrating the safety of ustekinumab in younger pediatric patients with psoriasis. In a retrospective case series by Klufas et al., ustekinumab was among the biologics evaluated for efficacy in treating pediatric psoriasis. They evaluated ustekinumab as monotherapy, as well as in combination with methotrexate. Six patients ranging from seven to eighteen years of age were treated with ustekinumab alone in varying doses: 1) four patients were given a fixed dose of 45 mg at weeks 0, 4, and every 12 weeks afterwards; 2) one patient received a fixed dose of 90 mg at weeks 0, 4, and every 12 weeks afterwards; 3) one patient received a fixed dose of 45 mg every 8 weeks. In all groups, Physician Global Assessment measurements decreased from 2.6 at baseline to 1.5 after a seven-month observation period. No significant adverse events were reported at any dosage.[7] Min et al. described a two-year old female with refractory psoriasis despite maximum topical therapy and phototherapy treated with ustekinumab. She received half-standard dosage (22.5 mg subcutaneously) ustekinumab at weeks 0 and 4, then every 12 weeks.[10]

In September 2016, ustekinumab was FDA approved for the treatment of Crohn's disease in adults 18 years and older. However, there is limited data on the efficacy or safety of ustekinumab in the treatment of pediatric Crohn's disease. There is one case of a 7-year-old male with refractory Crohn's disease, diagnosed at 9 months of age, treated successfully with half-dose ustekinumab, after failing azathioprine with steroids, mesalamine, methotrexate, and adalimumab.[8] In another retrospective case series of four patients ages 12 to 17 with refractory Crohn's disease, two of the four demonstrated a clinical response while the others had continued symptoms and disease complications, ultimately requiring discontinuation of therapy.[9]

Even less is published about treating concomitant psoriasis and Crohn's disease or TNF-induced psoriasis in patients with Crohn's disease. In a series of TNF-induced psoriasis in adults with inflammatory bowel disease, seven patients with underlying Crohn's disease were switched from anti-TNF therapy to ustekinumab with significant improvement in their skin lesions and maintenance of their bowel disease.[1] They found that anti-TNF-induced psoriasiform skin lesions were characterized by IL-17/IL-22 expressing Th17 cells and IFN-γ expressing Th1 cells, with increased expression of Th17 cells correlated with more severe skin lesions and a need for ustekinumab therapy.[1] There is only one other case in the literature of a pediatric patient with inflammatory bowel disease and TNF inhibitor-induced psoriasis treated with ustekinumab.[12] This was a 16 year old female with Crohn's disease who developed psoriasiform lesions after treatment with infliximab and adalimumab. She failed treatment with topical corticosteroids, was unable to tolerate methotrexate and was ultimately treated with ustekinumab with complete clearance of her skin lesions at 10 months and sustained remission of her Crohn's disease.

CONCLUSION

We present the first case of a school-age pediatric patient with TNF inhibitor-induced psoriasis treated with ustekinumab. She achieved complete clearance of her psoriasis, her alopecia resolved, and she has had maintenance of remission of her Crohn's disease with complete mucosal healing. We recommend consideration of treatment with ustekinumab in pediatric patients with inflammatory bowel disease and TNF inhibitor-induced psoriasis recalcitrant to other therapies. However, controlled and blinded studies are needed to elucidate the long-term efficacy and safety of this medication in the pediatric population, and its use remains unlabeled until such data is obtained.

DISCLOSURES

None of the authors have any perceived potential conflicts of interest and/or relationships with industry.

REFERENCES

1. Tillack, C., et al., Anti-TNF antibody-induced psoriasiform skin lesions in patients with inflammatory bowel disease are characterised by interferon-gamma-expressing Th1 cells and IL-17A/IL-22-expressing Th17 cells and respond to anti-IL-12/IL-23 antibody treatment. *Gut*. 2014; 63(4):567-77.
2. Ko, J.M., A.B. Gottlieb, and J.F. Kerbleski, Induction and exacerbation of psoriasis with TNF-blockade therapy: a review and analysis of 127 cases. *J Dermatolog Treat*. 2009;20(2):100-8

3. Rahier, J.F., et al., Severe skin lesions cause patients with inflammatory bowel disease to discontinue anti-tumor necrosis factor therapy. *Clin Gastroenterol Hepatol.* 2010;8(12):1048-55.
4. Cullen, G., et al., Psoriasis associated with anti-tumour necrosis factor therapy in inflammatory bowel disease: a new series and a review of 120 cases from the literature. *Aliment Pharmacol Ther.* 2011;34(11-12):1318-27.
5. Shmidt, E., et al., Psoriasis and palmoplantar pustulosis associated with tumor necrosis factor-alpha inhibitors: the Mayo Clinic experience, 1998 to 2010. *J Am Acad Dermatol.* 2012.67(5): 179-85.
6. Guerra, I., et al. Incidence, clinical characteristics, and management of psoriasis induced by anti-TNF therapy in patients with inflammatory bowel disease: a nationwide cohort study. *Inflamm Bowel Dis.* 2016;22(4):894-901.
7. Klufas, D.M., J.M. Wald, and B.E. Strober. Treatment of moderate to severe pediatric psoriasis: a retrospective case series. *Pediatr Dermatol.* 2016;33(2):142-9.
8. Rinawi, F., et al., Ustekinumab for resistant pediatric Crohn disease. *J Pediatr Gastroenterol Nutr.* 2016;62(4):34-5.
9. Bishop, C., et al. Ustekinumab in pediatric Crohn disease patients. *J Pediatr Gastroenterol Nutr.* 2016;63(3):348-51.
10. Min MS, Shroff A, Rose S, Lebwohl M, Guttman-Yassky E. Ustekinumab as therapy for psoriasis in a 2-year-old girl. *J Eur Acad Dermatol Venereol.* 2016;30(11):109-110.
11. Bertrand V, El Haite A, Carré D. Efficiency of ustekinumab in Crohn's disease with severe psoriasiform rash induced by biotherapies in an adolescent. *Pediatr Dermatol.* 2017;34(4): 214-215
12. Matsumoto S, Mashima H. Efficacy of ustekinumab against infliximab-induced psoriasis and arthritis associated with Crohn's disease. *Biologics.* 2018;19(12):69-73.

AUTHOR CORRESPONDENCE

Michael I. Gordon DO
E-mail:..... gordonmi99@gmail.com