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Treatment of CGD-associated colitis with the IL-23 blocker ustekinumab

Manish J. Butte, MD, PhD* [Assistant Professor],

Division of Allergy, Immunology, and Rheumatology, Department of Pediatrics, Stanford University

K. T. Park, MD, MS [Assistant Professor], and

Division of Gastroenterology, Department of Pediatrics, Stanford University

David B. Lewis, MD [Professor and Chief]

Division of Allergy, Immunology, and Rheumatology, Department of Pediatrics, Stanford University

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To the Editor

Normal neutrophilic activity converts oxygen into free radicals. The resulting “inflammatory hypoxia” protects intestinal epithelium by stimulating mucus production and regulating transcription of pro- and anti-inflammatory genes. In chronic granulomatous disease (CGD), however, these responses fall short (1). In addition, chronic infection leads to excessive IL-23 production by antigen presenting cells and promotes differentiation of inflammatory Th17 cells (2). Colitis is seen in ~50% of CGD patients, especially those with X-linked disease (3), possibly due to hyper-inflammatory processes such as these.

We followed a 14-year old boy with X-CGD, diagnosed in infancy after presenting with recurrent cervical lymphadenitis due to *Staphylococcus aureus*. His neutrophils showed no increase in dihydrorhodamine fluorescence upon stimulation, and a null mutation was genetically identified (*Cybb* gene, p.Arg290Ter). He developed chronic colitis at age 3, complicated by perirectal abscesses and requiring anal fistulotomy. His weight was consistently below 3% (z-score ~-5) and he had chronically low albumin (2–2.8 g/L). At age 14, his bone age was 8 y. His severe colitis withstood treatment with azathioprine, methotrexate, 6-mercaptopurine, GM-CSF, hydroxychloroquine, mesalamine, infliximab (stopped due to liver abscess), adalimumab, and corticosteroids (prednisone and budesonide (Entocort-EC)). Recurrent flare-ups necessitated total parenteral nutrition and parenteral, systemic corticosteroids. Biopsies consistently showed chronic active pan-colitis with cryptitis, crypt abscesses, and granuloma formation throughout childhood.

*Corresponding Author: 300 Pasteur Drive, Grant Building Room H307A, Stanford CA 94305. Tel: 650-721-1324. Fax: 650-498-6077. Manish.Butte@stanford.edu.

Ustekinumab was approved in 2009 by the FDA for psoriasis and psoriatic arthritis. This monoclonal antibody antagonizes binding of IL-12 and IL-23 to their receptors by binding the common p40 subunit of IL-12 and IL-23. A phase 2b trial showed subjects with Crohn's disease benefited from ustekinumab (4). We provided a subcutaneous dose of ustekinumab 45 mg (~2 mg/kg) every two weeks to determine the maximal benefit of the response to anti-IL-12p40 antagonism, with a switch to monthly dosing after four months. Within a month, his chelitis improved, his appetite dramatically increased, his diarrhea ceased completely, and his weight rose. Over two months, his serum albumin rose and reached 3.8 g/L (normal) for the first time in his life. His mild anemia (hemoglobin ~9 g/dL) prior to therapy improved slightly (10.3 g/dL one year later). He was able to significantly decrease his dose of Entocort-EC from 3 mg three times daily to 3 mg every other day.

He received prophylaxis with clindamycin, trimethoprim/sulfamethoxazole, and itraconazole; interferon-gamma had been discontinued years before due to an increase in colitic flares. The patient twice developed mucosal inflammation of the nares that grew methicillin-sensitive *S. aureus* and required treatment with topical retapamulin, oral rifampin, and surgical debridement. Fourteen months after starting ustekinumab, he developed dyspnea, chest pain, and fevers. Chest CT revealed enlarged, necrotic, low-density hilar lymph nodes and >15 parenchymal mass-like opacities with adjacent ground-glass halos; there was no effusion or pleural thickening. He was admitted and treated with antibiotics (meropenem), antifungals (caspofungin and voriconazole), and oxygen with rapid defervescence and clinical improvement. Blood cultures did not reveal an organism, an unfortunately common occurrence in CGD (5). Ustekinumab was discontinued because of this infectious complication. Subsequently, his colitis returned. Intermittent bleeding in the stools (2–3 episodes over 5 months) began approximately four months later. There was a significant increase in bleeding and diarrhea 13 months after discontinuation of ustekinumab necessitating an increase in Entocort-EC to 3 mg twice daily. His albumin has been consistently below normal for the past three years. Current biopsies show chronic focally active colitis with granuloma formation, with no evidence of eosinophilia, CMV, acid fast bacilli, or fungi. Pigmented histiocytes were easily identified in the mucosa and submucosa, as is typically seen in CGD-associated colitis.

In summary, therapy with ustekinumab eliminated colitis in this subject, though the improvement was not durable after stopping treatment. In the CGD-associated colitis of humans and murine models, hyper-inflammation has been associated with elevations of interferon gamma, IL-17A, and IL-21, suggesting the involvement of Th17 and Th1 cells (6–8). TNF production is also likely important in CGD-associated colitis, though TNF blockade in CGD reduced colitis, it was associated with fatal complications in 2 out of 5 patients in one study (9). Ustekinumab impedes development of both Th17 (by blocking IL-23) and Th1 cells (by blocking IL-12), though monoclonal therapy that blocks IL-17A alone merits consideration. In Crohn's disease, the rate of infections was no different between subjects treated with ustekinumab and placebo (10). However, in CGD-associated colitis, we recommend vigilance while on therapy. A lower dose of 1 mg/kg (10) or less may improve the tradeoff between increasing infection susceptibility and reducing intestinal inflammation.

References

1. Campbell EL, Bruyninckx WJ, Kelly CJ, Glover LE, McNamee EN, Bowers BE, et al. Transmigrating neutrophils shape the mucosal microenvironment through localized oxygen depletion to influence resolution of inflammation. *Immunity*. 2014; 40(1):66–77. [PubMed: 24412613]
2. Horvath R, Rozkova D, Lastovicka J, Polouckova A, Sedlacek P, Sediva A, et al. Expansion of T helper type 17 lymphocytes in patients with chronic granulomatous disease. *Clinical and experimental immunology*. 2011; 166(1):26–33. [PubMed: 21910722]
3. Marciano BE, Rosenzweig SD, Kleiner DE, Anderson VL, Darnell DN, Anaya-O'Brien S, et al. Gastrointestinal involvement in chronic granulomatous disease. *Pediatrics*. 2004; 114(2):462–8. [PubMed: 15286231]
4. Sandborn WJ, Gasink C, Gao L-L, Blank M, Johanns J, Guzzo C, et al. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase2b Study of Ustekinumab, a Human Monoclonal Antibody to IL-12/23p40, in Patients With Moderately to Severely Active Crohn's Disease: Results Through Week 22 From the Certifi Trial. *Gastroenterology*. 140(5):S-109.
5. Song E, Jaishankar GB, Saleh H, Jithpratuck W, Sahni R, Krishnaswamy G. Chronic granulomatous disease: a review of the infectious and inflammatory complications. *Clin Mol Allergy*. 2011; 9(1): 10. [PubMed: 21624140]
6. Rodrigues-Sousa T, Ladeirinha AF, Santiago AR, Carvalheiro H, Raposo B, Alarcao A, et al. Deficient production of reactive oxygen species leads to severe chronic DSS-induced colitis in Ncf1/p47phox-mutant mice. *Plos One*. 2014; 9(5):e97532. [PubMed: 24873968]
7. Kuijpers T, Lutter R. Inflammation and repeated infections in CGD: two sides of a coin. *Cellular and molecular life sciences: CMLS*. 2012; 69(1):7–15. [PubMed: 22083605]
8. Rieber N, Hector A, Kuijpers T, Roos D, Hartl D. Current concepts of hyperinflammation in chronic granulomatous disease. *Clinical & developmental immunology*. 2012; 2012:252460. [PubMed: 21808651]
9. Uzel G, Orange JS, Poliak N, Marciano BE, Heller T, Holland SM. Complications of tumor necrosis factor-alpha blockade in chronic granulomatous disease-related colitis. *Clin Infect Dis*. 2010; 51(12):1429–34. [PubMed: 21058909]
10. Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *The New England journal of medicine*. 2012; 367(16):1519–28. [PubMed: 23075178]