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Sent via email to: AndersonK7@aetna.com, PritzkerJ@AETNA.com

Dear Dr. Anderson and Dr. Pritzker

The undersigned organizations are writing to bring to your attention our collective, serious concerns regarding your policy for dosing restrictions of infliximab for the treatment of our patients with Inflammatory Bowel Disease (IBD) which includes both Crohn's disease and ulcerative colitis. Specifically, we are concerned the policy is not driven by, nor consistent with, current literature or our clinical experience and will have a negative effect on our ability to provide medically necessary care.

Increasingly, our physician members are being told Aetna will only allow infliximab dosing of 5mg/kg every eight weeks for our pediatric and adult patients. This dosing restriction is occurring even in situations where the patient has historically successfully required a higher maintenance dose. In 1998, the Food and Drug Administration (FDA) approved the use of infliximab in patients with Crohn's disease. Since that time, clinicians have learned, based on an overwhelming amount of data, that the 5mg/kg dosing level is frequently insufficient to achieve active disease resolution and clinical remission, and that targeting drug levels through therapeutic drug monitoring is critical and medically necessary to provide effective treatment for our patients with Crohn's disease and ulcerative colitis.

Published data on therapeutic drug monitoring of patients with IBD from a number of different studies, including randomized controlled, prospective, retrospective, multi-center and real-life quality improvement clinical trials, suggest that to achieve a clinically effective therapeutic drug level, 10 mg/kg or greater is often necessary for infliximab. Further, there is an overwhelming amount of medical literature that affirms the FDA-approved dose is not adequate for most children and adults with IBD. In addition, it is important to note the original FDA labeling published in 1998 has not been updated or revised with the subsequently obtained data. That literature, affirming that drug dosing of ≥5 mg/kg to achieve clinical remission, is supported by therapeutic drug monitoring that ensures adequate doses are administered to prevent a patient from losing their clinical response to treatment, developing drug antibodies or having a potentially fatal infusion reaction.

The current practice by Aetna of requiring physicians to uniformly decrease dosing to 5mg/kg is putting our pediatric and adult patients at risk of losing their effective medication response which could result in long-term or potentially lifetime negative and serious or disabling consequences. In addition, the dose reduction will result in exacerbations and flares of disease and subsequently otherwise costly avoidable emergency department visits, hospitalizations, unnecessary surgery, narcotic and steroid use, the need for alternate biologic therapies, as well as adverse psychosocial effects. In summary, the 5mg/kg dose for the pediatric and adult population with IBD has been proven to be ineffective since the initial FDA approval and labeling in 1998. Dosing of 10 mg/kg (or above) has been shown to be both clinically effective at achieving remission and may be necessary to achieve therapeutic drug levels. The requirement by Aetna to use 5 mg/kg dosing based on the initial FDA label should be rescinded to allow physicians to make clinical decisions in the best interest of their patients.

Our organizations are urgently requesting a meeting with you to further discuss this very troublesome policy that will clearly result in negative patient outcomes if it is not immediately addressed. Please find references for supporting literature below.

To arrange a virtual meeting, please contact Camille Bonta (NASPGHAN) at cbonta@summithealthconsulting.com, Leslie Narramore (AGA) at lnarramore@gastro.org, Brand Conway (ACG) at BConway@gi.org, Lakitia Mayo (ASGE) at lmayo@asge.org, and Teresa Salaway (AAP) at tsalaway@aap.org.

Sincerely,

American Academy of Pediatrics
American College of Gastroenterology
American Gastroenterological Association
American Society for Gastrointestinal Endoscopy
North American Society for Pediatric Gastroenterology Hepatology and Nutrition

References:

Clarkston K, Tsai Y, Jackson K, et al. Development of Infliximab Target Concentrations During Induction in Pediatric Crohn Disease Patients. J Pediatr Gastroenterol Nutr. 2019, Jul;69(1):68-74.

Colman R, Tsai Y, Jackson K, et al. Achieving Target Infliximab Drug Concentrations Improves Blood and Fecal Neutrophil Biomarkers in Crohn's Disease. Inflamm Bowel Dis. 2021 Jun 15;27(7):1045-1051.

Gemayel NC, Rizzello E, Atanasov P, Wirth D, Borsi A. Dose escalation and switching of biologics in ulcerative colitis: a systematic literature review in real-world evidence. Current medical research and opinion. 2019 Nov 2;35(11):1911-23.

Guberna L, Nyssen OP, Chaparro M, Gisbert JP. Frequency and Effectiveness of Empirical Anti-TNF Dose Intensification in Inflammatory Bowel Disease: Systematic Review with Meta-Analysis. Journal of Clinical Medicine. 2021 Jan;10(10):2132.

Guido A, Crandall W, E Homan, et al. Improving Post-induction Antitumor Necrosis Factor Therapeutic Drug Monitoring in Pediatric Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr. 2020 Jan;70(1):48-54.

Hellmann J, Etter R, Denson L, et al. Quality Improvement Methodology Optimizes Infliximab Levels in Pediatric Patients with Inflammatory Bowel Disease. Pediatr Qual Saf. 2021 May 5;6(3):e400. eCollection May-Jun 2021.

Jongsma M, Winter D, Huynh H, et al. Infliximab in young paediatric IBD patients: it is all about the dosing. Paediatric IBD Porto Group of ESPGHAN. Eur J Pediatr. 2020 Dec;179(12):1935-1944. Epub 2020 Aug 19.

Kósa F, Kunovszki P, Borsi A, Iliás Á, Palatka K, Szamosi T, Vincze Á, Molnár T, Lakatos PL. Anti-TNF dose escalation and drug sustainability in Crohn's disease: Data from the nationwide administrative database in Hungary. Digestive and Liver Disease. 2020 Mar 1;52(3):274-80.

Mattoo VY, Basnayake C, Connell WR, Ding N, Kamm MA, Lust M, Niewiadomski O, Thompson A, Wright EK. Systematic review: efficacy of escalated maintenance anti-tumour necrosis factor therapy in Crohn's disease. Alimentary Pharmacology & Therapeutics. 2021 Jun 21.

Minar P, Saeed S, Afreen M, et al. Practical Use of Infliximab Concentration Monitoring in Pediatric Crohn Disease. J Pediatr Gastroenterol Nutr. 2016 May;62(5):715-22.

Shin JY, Park HM, Lee MY, Jeon JY, Yoo HJ, Ye BD. Real-World Incidence of Suboptimal Response to Anti-Tumor Necrosis Factor Therapy for Ulcerative Colitis: A Nationwide Population-Based Study. Gut and Liver. 2021 Apr 2.

Winter D, Joosse M, de Wildt, S, et al. Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Infliximab in Pediatric Inflammatory Bowel Disease: A Systematic Review and Revised Dosing Considerations . J Pediatr Gastroenterol Nutr. 2020 Jun;70(6):763-776.