# CONFER Cases Round 11

Description

## Case 1

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| **Case Title** | Anti-TNF induced sarcoidosis in Inflammatory Bowel Diseases |
| **Principal Investigator** | Carla Felice |
| **Case Manager** | Julien Kirchgesner |
| **Case Description** | A 55 years-old male patient presented with a history of diarrhea, abdominal pain and arthralgia since August 2021. A colonoscopy with biopsy confirmed the suspicion of active ulcerative colitis (UC), initially treated by oral beclomethasone and mesalazine. After few months, the patient developed pruritus and liver enzymes abnormalities [AST 354 U/l (ULN, upper limit of normal 35), ALT 289 U/l (ULN 45), GGT 2304 U/l (ULN 61)] which prompt suspicion of sclerosing cholangitis, confirmed by cholangio-MR (magnetic resonance). Ursodeoxycolic acid was started. Since UC became steroid-dependent, infliximab was started in November 2022 obtaining stable clinical remission and mucosal healing. In April 2023, after 6 months of anti-TNF (tumor necrosis factor) therapy, a new cholangio-MR showed a liver inflammatory lesion and a pulmonary consolidation. Chest CT scan and subsequent PET-CT showed ilo-mediastinal lymphadenomegaly with moderate caption (MAX SUV 15) with no respiratory or systemic symptoms. Bronchoalveolar lavage fluid test excluded mycobacteriosis. At EBUS-TBNA of mediastinal lymph nodes a granuloma was identified, confirming the diagnosis of sarcoidosis. Infliximab was switched to vedolizumab maintaining clinical and endoscopic remission. PET-CT and cholangio-MR repeated in July 2024 showed reduction in dimension and caption of both pulmonary nodules and liver inflammatory area. |
| **Main Clinical Question** | - What is the median time occurring from anti-TNF therapy start and development of sarcoidosis?<br>- What are the most typical presentations?<br>- What are the risk factors for developing such a condition?<br>- What is the best way to manage anti-TNF induced sarcoidosis? |
| **Literature on the topic** | Sarcoidosis is a rare paradoxical reaction to anti-TNF agents. Most cases are described in patients with rheumatological diseases. In 2020, in a literature review, 85 patients with anti-TNF induced sarcoidosis have been described, including 11 patients with inflammatory bowel diseases (IBD). The most frequent anti-TNF agents were Etanercept (N=45), Adalimumab (N=21), Infliximab (N=17) and Certolizumab (N=2). In this analysis, 81/85 patients presented resolution of symptoms during follow-up after discontinuation of anti-TNF and addition of steroids in symptomatic patients (Koda 2020).<br>So far, 17 cases of anti-TNF induced sarcoidosis in IBD have been described (tab. 1). A diagnosis of Crohn's disease was more frequent (76%) than UC. The culprit drugs were infliximab (59%) and adalimumab (41%) with median duration of anti-TNF therapy of 2.0 years (interquartile 1-5, range 0.58-15) before sarcoidosis development. Systemic symptoms were described in 9/17 (53%). The lungs (including hilar-mediastinal lymphadenopathy) were involved in 14/17 (82%), the skin in 6/17 (35%) and liver/spleen in 3/17 (18%). In single reports also cardiac, neurological, ocular, renal and oral mucosa involvement were reported. The diagnosis was established through histological demonstration of granulomas in all cases, except |

one. The anti-TNF treatment was withheld in 11/17 patients (65%) and additional treatment with steroids was required in 8/11; methotrexate and hydroxycloroquine were added in one case. Interestingly, 5/17 patients (35%) continue anti-TNF despite the paradoxical sarcoidosis, only adding steroid treatment with clinical benefit.

The clinical picture of this rare condition varies widely. The collection of further cases will help to identify possible risk factors for the development of anti-TNF induced sarcoidosis and to better define the optimal therapeutic management.

**[Table 1]**

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**Table 1. Characteristics of the IBD cases described in the literature.**

| NR | IBD | Sex | Anti-TNF/ age (Y) | Time to sarcoidosis (Y) | SS | Organ involvement | Histology | anti-TNF stop | Added Therapy | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | CD | M | Ada/30 | 5 | Yes | Lung/Skin/ Uveitis | Yes | Yes | Steroids | Decock 2017 |
| **2** | CD | M | Ada/21 | 1,5 | No | Lung/Skin/ Heart | Yes | Yes | Steroids, HCQ | Decock 2017 |
| **3** | CD | F | Ifx/44 | 5 | No | CNS | Yes | Yes | Steroids | Simonetto 2015 |
| **4** | CD | M | Ada/37 | 2 | No | Lung/Skin | No | Yes | Steroids, MTX | Mc Donnell 2014 |
| **5** | CD | F | Ada/25 | 1,5 | No | Lung/Spleen | Yes | No | Steroids | Kotze 2013 |
| **6** | CD | M | Ifx/35 | 0,58 | Yes | Lung/Skin | Yes | No | No | Takahashi 2010 |
| **7** | CD | F | Ada/49 | 10 | No | Oral | Yes | No | Steroid | Simonato 2023 |
| **8** | CD | F | Ifx/35 | 1 | Yes | Lung/Liver | Yes | Yes | Steroid | Chebli 2024 |
| **9** | CD | F | Ifx/37 | 15 | Yes | Lung/Liver | Yes | Yes | No | Kashima 2021 |
| **10** | CD | M | Ifx/18 | 2 | Yes | Lung | Yes | Yes | No | Okoshi 2020 |
| **11** | UC | F | Ifx/66 | 2,3 | No | Skin | Yes | No | Steroid | Fok 2012 |
| **12** | UC | M | Ifx/30 | 3,8 | Yes | Lung/Sub | Yes | Yes | Steroid | Gîlcă 2017 |
| **13** | UC | M | Ada/42 | 1 | Yes | Lung/Kidney/ Gut | Yes | Yes | Steroid | Villemaire 2014 |
| **14** | CD | M | Ifx/28 | 0,67 | No | Lung | Yes | Yes (Temporary) | No | Kim 2017 |
| **15** | CD | M | Ifx/34 | 10,67 | Yes | Lung/Skin | Yes | No | No | Numakura 2016 |
| **16** | CD | F | Ifx/57 | 6 | Yes | Lung | Yes | Yes | Steroids | Fuentes 2021 |
| **17** | UC | F | Ada/42 | 1 | Yes | Lung/Skin | Yes | No | Steroid | Arenas Aravena 2024 |

Abbreviations: IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; M=male; F=female; Y=year; Ada=adalimumab; Ifx=infliximab; SS: systemic symptoms; CNS=Central nervous system; Sub=subdiaphragmatic lymphnodes;

ECCO CONFER Cases

## Case 2

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| **Case Title** | Effectiveness and Safety of Ozanimod and Natalizumab in Patients with Coexisting Inflammatory Bowel Disease and Multiple Sclerosis |
| **Principal Investigator** | Marie Truyens |
| **Case Manager** | Mette Julsgaard |
| **Case Description** | Patients with both inflammatory bowel disease (IBD) and multiple sclerosis (MS) present unique therapeutic challenges due to overlapping immune mechanisms and the complex safety profiles of immunomodulatory treatments. While both ozanimod and natalizumab, selective immunomodulators, have demonstrated efficacy in managing IBD and MS individually, their effectiveness in patients with concurrent IBD and MS has yet to be comprehensively evaluated. Natalizumab, a monoclonal antibody that targets the α4-subunit of both α4β1 and α4β7 integrins has proven effectiveness in<br>reducing MS relapse rates (1) as well as inducing remission in Crohn's disease (CD) (2, 3). However, its association with progressive multifocal leukoencephalopathy (PML) and the availability of alternative agents that are not associated with PML have limited the use of natalizumab for CD.<br>Currently, in Europe, natalizumab is only approved for MS (3). Ozanimod, an oral sphingosine 1-phosphate receptor modulator (S1PR), has demonstrated promising results in managing moderate-to-severe ulcerative colitis (UC) (4) and relapsing-remitting MS (5), and is approved in Europe for bothconditions. |
| **Main Clinical Question** | This CONFER case aims to evaluate the effectiveness and safety profiles of ozanimod and natalizumab in patients with concurrent IBD and MS. The study will focus on disease activity, relapse rates, and adverse events of both diseases under treatment with one of these molecules. By examining real-world data across multiple centers, this study seeks to provide valuable insights into the optimal management of this complex patient population, guiding therapeutic decisions. |
| **Literature on the topic** | Several studies have confirmed the effectiveness of ozanimod and natalizumab for both IBD as well as MS (1, 3-6), but to our knowledge, no studies have specifically assessed outcomes in patients with concurrent IBD and MS.<br>**References:**<br>1. Brandstadter R, Katz Sand I. The use of natalizumab for multiple sclerosis. Neuropsychiatric Disease and Treatment. 2017;13(null):1691-702.<br>2. Pagnini C, Arseneau KO, Cominelli F. Natalizumab in the treatment of Crohn's disease patients. Expert Opinion on Biological Therapy. 2017;17(11):1433-8.<br>3. Nelson SML, Nguyen TM, McDonald JWD, MacDonald JK. Natalizumab for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews. 2018(8).<br>4. Sandborn WJ, Feagan BG, D'Haens G, Wolf DC, Jovanovic I, Hanauer SB, et al. Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis. New England Journal of Medicine. 2021;385(14):1280-91.<br>5. Lassiter G, Melancon C, Rooney T, Murat A-M, Kaye JS, Kaye AM, et al. Ozanimod to Treat Relapsing Forms of Multiple Sclerosis: A Comprehensive Review of Disease, Drug Efficacy and Side Effects. Neurology International. 2020;12(3):89-108.<br>6. Rubin DT, Cree BAC, Wolf DC, Alekseeva O, Charles L, Petersen A, et al. S911 Long-Term Safety of Ozanimod in |

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