SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET		
		Day	Month	Year				Day	Month	Year
PRIVACY	ISRAEL		PRIVACY		15 Years	Unk	Unk		Unk	

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant, Medically Significant
Infusion reaction to infliximab [Infusion related reaction]
eczema [Eczema]
Cellulitis [Cellulitis]
skin absces [Abscess]
Nonspecific rash [Rash]
elevated liver enzymes for Adalimumab + ustekinumab [Hepatic enzyme increased]
COVID-19 infection [COVID-19]
Clostridioides difficile infection [Clostridium difficile infection]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☒ LIFE THREATENING
- ☐ CONGENITAL ANOMALY
- ☒ OTHER: Medically Significant

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Infliximab (INFLIXIMAB) Unknown {Lot # Unknown}
#2) Adalimumab (ADALIMUMAB) Solution for injection {Lot # Unknown} **(Continued on Additional Information Page)**

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) Unknown	#1) Unknown
#2) Unknown	#2) Unknown

17. INDICATION(S) FOR USE
#1) Pediatric IBD (Inflammatory bowel disease)
#2) Pediatric IBD (Inflammatory bowel disease)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) Unknown	#1) Unknown
#2) Unknown	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)
From/To Dates | Type of History / Notes | Description
Unknown

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Celltrion Inc.
13-3 Songdo-dong,
Yeonsu-gu, Incheon 406-840
KOREA, REPUBLIC OF

26. REMARKS
Medically Confirmed: Yes

24b. MFR CONTROL NO.
2023IL007996

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
13-APR-2023

24d. REPORT SOURCE
☐ STUDY ☒ LITERATURE ☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
19-APR-2023

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

influenza-like disease [Influenza like illness]
mycoplasma upper respiratory tract infection [Upper respiratory tract infection]
sinusitis [Sinusitis]
headache [Headache]
elevated liver enzymes from Infliximab + vedolizumab [Hepatic enzyme increased]
External otitis [Ear infection]
psoriasis [Psoriasis]
urticaria [Urticaria]
folliculitis [Folliculitis]
fever [Pyrexia]
impetigo [Impetigo]
Rash [Rash]
Mycoplasma infection [Mycoplasma infection]

Case Description: This initial serious literature report was received from a healthcare professional in Israel on 13 Apr 2023: Yerushalmy-Feler A, Olbjorn C, Kolho KL, Aloi, M, Musto F, Martin-de-Carpi J, et al. Dual Biologic or Small Molecule Therapy in Refractory Pediatric Inflammatory Bowel Disease (DOUBLE-PIBD): A Multicenter Study from the Pediatric IBD Porto Group of ESPGHAN. Inflammatory Bowel Diseases. 2023; XX; 1-8.

The aim of this study was to evaluate the effectiveness and safety of dual biologics or combination of biologics and JAK inhibitor therapy in a larger than previously reported cohort of pediatric patients with IBD.

This was a retrospective cohort study from 14 centers affiliated with the Pediatric IBD Interest and Porto groups of European to be significant in the univariate analysis. All analyses were performed in the intention-to-treat population.

This case refers to male and female patients with a median age of 15 who experienced Infusion reaction to infliximab, cellulitis, skin abscess, mycoplasma upper respiratory tract infection, clostridioides difficile infection, sinusitis, impetigo, external otitis, cellulitis, urticaria, nonspecific rash, elevated liver enzymes, COVID-19 infection, influenza-like disease, headache, psoriasis, folliculitis, and eczema following therapy with Infliximab and Adalimumab.

The patient received Infliximab and Adalimumab both at unspecified dose, frequency, and route for pediatric IBD on unspecified therapy dates. Batch/lot numbers was not reported.

Co-suspect drugs included Vedolizumab, Ustekinumab, Corticosteroids, 5-ASA, 6-MP, Azathioprine, Methotrexate, Tofacitinib; all at unspecified dose, frequency, and route for pediatric IBD on unspecified therapy dates. Batch/lot numbers was not reported.

On unspecified dates, the patient's experienced Infusion reaction to infliximab, cellulitis, skin abscess, mycoplasma upper respiratory tract infection (coded to mycoplasma infection and upper respiratory tract infection), clostridioides difficile infection, sinusitis, impetigo, external otitis, cellulitis, urticaria, nonspecific rash (serious and non-serious), elevated liver enzymes, COVID-19 infection, influenza-like disease, headache, psoriasis, folliculitis, and eczema. Corrective treatment for the events, action taken with Infliximab and Adalimumab, and outcome of the events was not reported.

The patients relevant medical history, past and concomitant medications were not reported.

The authors concluded that this study demonstrated that a combination of 2 biologics or a biologic with small molecule therapy may be effective in children with refractory IBD. The efficacy should be weighed against the risk of serious adverse events. The ideal selection of dual biologic regimens remains to be determined.

The reporter assessed the events Infusion reaction to infliximab, cellulitis, skin abscess, nonspecific rash, elevated liver enzymes, and eczema as serious (life threatening). Causality of events were not reported. Furthermore, medically significant was added as seriousness criteria for events cellulitis and Clostridium difficile infection as these were IME terms and COVID-19 as it is in ASL.

Case comment: For Infliximab: Causality of Infusion related reaction, Eczema, Cellulitis, Abscess, Rash, COVID-19, Clostridium difficile infection (listed, serious), Hepatic enzyme increased, Upper respiratory tract infection, Mycoplasma infection, Influenza like illness, Sinusitis, Headache, Psoriasis, Ear infection, Urticaria (listed, non-serious) is related due to temporal relationship between onset of event and reported therapy. Causality of Hepatic enzyme increased (listed, serious) Rash, Pyrexia, Impetigo, Folliculitis (listed, non-serious) is not related as event is attributed to Adalimumab use. For Adalimumab: Causality of Hepatic enzyme increased, COVID-19 (listed, serious), Influenza like illness (unlisted, non-serious), Rash, Headache, Pyrexia, Impetigo, Folliculitis, Psoriasis (listed, non-serious) is related due to temporal relationship between onset of event and reported therapy. Causality of Infusion related reaction (unlisted, serious), Eczema, Cellulitis, Abscess, Rash, Clostridium difficile infection (listed, serious), Hepatic enzyme increased, Upper respiratory tract infection, Mycoplasma infection, Sinusitis, Ear infection, Urticaria (listed, non-serious) is not related as event is attributed to Infliximab use. The concomitant use of vedolizumab and ustekinumab confounds the medical assessment.

Mfr. Control Number: 2023IL007996

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#3) VEDOLIZUMAB (VEDOLIZUMAB) {Lot # Unknown}; Regimen #1	Unknown; Unknown	Pediatric IBD (Inflammatory bowel disease)	Unknown; Unknown
#4) USTEKINUMAB (USTEKINUMAB) {Lot # Unknown}; Regimen #1	Unknown; Unknown	Pediatric IBD (Inflammatory bowel disease)	Unknown; Unknown
#5) TOFACITINIB (TOFACITINIB) {Lot # Unknown}; Regimen #1	Unknown; Unknown	Pediatric IBD (Inflammatory bowel disease)	Unknown; Unknown
#6) CORTICOSTEROIDS {Lot # Unknown}; Regimen #1	Unknown; Unknown	Pediatric IBD (Inflammatory bowel disease)	Unknown; Unknown
#7) 5-ASA (5-ASA) {Lot # Unknown}; Regimen #1	Unknown; Unknown	Pediatric IBD (Inflammatory bowel disease)	Unknown; Unknown
#8) 6-MERCAPTOPURINE MONOHYDRATE (6-MERCAPTOPURINE MONOHYDRATE) {Lot # Unknown}; Regimen #1	Unknown; Unknown	Pediatric IBD (Inflammatory bowel disease)	Unknown; Unknown
#9) AZATHIOPRINE (AZATHIOPRINE) {Lot # Unknown}; Regimen #1	Unknown; Unknown	Pediatric IBD (Inflammatory bowel disease)	Unknown; Unknown
#10) METHOTREXATE (METHOTREXATE) {Lot # Unknown}; Regimen #1	Unknown; Unknown	Pediatric IBD (Inflammatory bowel disease)	Unknown; Unknown

24d. Report Source Literature
Journal: Inflammatory Bowel Diseases
Author: Yerushalmy-Feler A, Olbjorn C, Kolho KL, Aloi M, Musto F, Martin-de-Carpi J, et al.
Title: Dual Biologic or Small Molecule Therapy in Refractory Pediatric Inflammatory Bowel Disease (DOUBLE-PIBD): Multicenter Study from the Pediatric IBD Porto Group of ESPGHAN
Volume: XX Year: 2023 Pages: 1-8