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Special Article-Inflammatory Bowel Disease

Safety Profile of Anti-TNF Agents in Polish Pediatric Patients with Crohn's Disease

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Abstract

Back ground: In recent years, monoclonal antibodies against TNF-alpha, infliximab (IFX) and Adalimumab, have been gaining increasing popularity in Crohn's disease (CD) management. Many clinical trials have shown that biologics are generally well-tolerated and safe. However, the follow-up time with regards to safety is too short and data on that issue are still limited. The aim of this study was to analyze the cumulative safety profile of biologic therapy with IFX and/or ADA, documented during up to 8-year follow-up of Polish children with moderately to severely active CD.

Patients and Methods: We have performed a retrospective analysis of 110 children, mean age 13.0 ±9.3 years, diagnosed with CD and treated with IFX and/or ADA within the period of 8 years, between 2005 and 2013. Safety data for all treated patients, collected throughout the entire treatment period, were included in the safety analyses.

Results: A total of 67 treatment related adverse events (TRAEs) were recorded, including 43 (64.17%) for IFX and 24 (35.83%) for ADA. The majority of TEAEs were mild-to-moderate in intensity. The most frequently reported TEAEs included anemia (n=17, 20.23% for IFX and n=9, 23.08% for ADA) and mild infections (n=9, 10.7% for IFX and n=5, 12.8% for ADA). No serious adverse events (sAEs) were documented.

Conclusion: Biologic therapy with infliximab and/or Adalimumab is generally well-tolerated and safe, and does carry the risk of sAEs.

Keywords: Biologic therapy; Safety; Crohn's disease; Children

Introduction

Crohn's disease (CD) is an inflammatory condition of unknown etiology, which is classified in the inflammatory bowel disease (IBD) group, along with ulcerative colitis (UC) [1]. Since no effective CD treatment protocol has been developed [1]. The goals of both the pharmacotherapy and surgical management are limited to obtaining the longest possible remission and preventing relapse [1].

In recent years, however, the advent of biological drugs has had a significant impact on the management of IBD. Many clinical trials have demonstrated the efficacy and safety of monoclonal antibodies against tumor necrosis factor (TNF), Infliximab (IFX) and Adalimumab (ADA), in both induction [1] and maintenance [1] of clinical remission. Moreover, treatment with biologics was also revealed to result in endoscopic healing [1,2], which points to a possibility of longer clinical remission [3].

Nonetheless, the use of biologic agents is still limited, mostly due to high cost and uncertainty about long-term safety. The safety issue is especially important. Although biologics are generally considered a well-tolerated and safe therapy, the follow-up time with regards to safety is too short and the available data are still limited. The safety concerns associated with biologic therapies include increased risk of infections, autoimmune conditions, lymphomas, demyelinating diseases, and exacerbation of heart failure [4-6]. Reactivation of mycobacterium infections has also been reported in patients treated with anti-TNF agents [7].

The monoclonal antibodies used for anti-TNF therapy frequently induce formation of antibodies against infliximab (ATI) and Adalimumab (ATA). The presence of these antibodies was associated with a shorter duration of response to therapy and a higher incidence of infusion reactions [8].

The safety of IFX has been evaluated by the TREAT registry, which was established to study the long-term safety of this biologic agent and other therapies in prospectively followed patients with CD [9]. A total of 6,290 patients (3,179 IFX recipients and 3,111 recipients of other therapies) have been enrolled in this registry since August 2004. According to the available data, the general overall safety of IFX is similar to that of conventional immune modulator agents (IMMs) [9,10].

Nonetheless, the data from Central Europe concerning the safety of biologic therapy, especially ADA, are still limited. Therefore, the aim of this study was to analyze the cumulative safety profile of biologic treatment with IFX and/or ADA in Polish children with moderately to severely active CD.

Patients and Methods

Patients

A retrospective analysis of children with moderately to severely

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active CD, treated with biologic therapy with either IFX and/or ADA at the Department of Gastroenterology, Hepatology and Feeding Disorders, Children's Memorial Health Institute in Warsaw (Poland), was conducted. The analysis included the 8-year period between 2005 and 2013.

Patients were qualified to biological therapy on the basis of a high disease activity index – Pediatric Crohn's disease activity index (PCDAI) >30 and a lack of response to conventional therapy including steroids and immune modulators. The patients received IFX induction therapy (5 mg/kg) at weeks 0, 2, and 6. Additionally, all patients were receiving concomitant immune modulator therapy using azathioprine or methotrexate due to severe course of the disease. On week 10, the therapeutic responses were evaluated on the basis of PCDAI score and endoscopic examination. Patients with the clinical response were qualified on maintenance therapy. Clinical response was defined as a decrease in PCDAI score by ≥15 points and final PCDAI score lower than 30 points, and clinical remission defined as PCDAI ≤10 points. Five patients were primary non-responders.

Safety evaluation

Adverse events (AEs) were monitored throughout the entire treatment period. At each visit, AEs were documented, and blood samples were obtained for clinical laboratory evaluations. Safety data were reported for all patients, by prior biologic use, as well as by concomitant IMM and corticosteroid use at baseline of biologic therapy, and were included in the safety analyses. AEs that occurred on or after the first biologic agent dose and up to 70 days after the last dose thereof were considered treatment-emergent AEs (TEAEs). Clinical data analyzed during follow-up were gathered from both medical records and documentation, the database was created and statistical analysis was performed.

Serious AE (sAE) was defined as any adverse event occurring that results in any of the following outcomes: death, a life-threatening adverse event, requires inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/ incapacity, or a congenital anomaly/birth defect. Mild AE was defined as an experience that was transient and required no special treatment or intervention, and did not interfere with usual daily activities, including transient laboratory test alterations. Serious infection was defined as (invasive) infection requiring intra venous or oral antibiotics and/or any infection requiring hospitalization, if outpatient at onset. Mild infections included ssubtle infections of low intensity, which did not require antibiotics, such as viral upper respiratory tract infections.

Results

A total of 67 TRAEs were recorded in all 110 patients, among them 43 (64.17%) events for IFX and 24 (35.83%) for ADA. Eight patients (7.3%) discontinued therapy, 5 of them were primary non-responders while 3 children had AEs (leucopenia) which disqualified them from therapy. The mean duration of follow-up was 5 years. Table 1 presents detailed characteristics of CD patients treated with biologic therapy.

The most common TRAEs included anemia (n=17, 20.23% for IFX and n=9, 23.08% for ADA) and mild infections (n=9, 10.7% for IFX and n=5, 12.8% for ADA). Upper respiratory tract infections were the most frequently reported infections for IFX, and gastro-intestinal infections for ADA, with the frequencies of 4/9 (44.44%) and 2/5 (40.0%), respectively. No serious infections were documented. Similarly, no deaths, malignancies, demyelinating disorders of the central nervous system, optic neuritis, or seizures were recorded throughout the biologic therapy period. Infusion reactions were reported in 3 IFX patients (4.5%). No cases of serum sickness-like reactions or possible delayed hypersensitivity reactions were noted, and none of the AE necessitated the termination of therapy. Data on the total exposure to IFX and ADA are presented in Table 2.

Table 1: Detailed characteristics of CD patients treated with biologic therapy (n=110).

Parameter	Characteristic
Gender:	
- males	54 (50.5%)
- females	53 (49.5%)
Age (years)	13.0±9.3
Mean duration time of disease (years)	8.4±7.3
PCDAI	52.5±27.5
Involved region:	
- caecum (L1)	12.1%
- left-side (L2)	31.8%
- ileocolon (L3)	56.1%
- upper disease (L4)	14.8%
Behaviour	
- B1	93 (84.5%)
- B2	2 (1.9%)
- B3	15 (13.6%)
SES-CD (ranges)	18 (0;22)
Extraintestinal manifestations (18)	
- arthralgia/arthitis	14/18 (77.8%)
- osteoporosis	2/18 (11.1%)
- erythema nodosum	2/18 (11.1%)
Concomitanttreatment	
- AZA	52 (38.2%)
- MTX	9 (8.2%)
- GKS	59 (53.6%)

Abbriviations: AZA: Azathiopryne; MTX: Methotrexate; GKS: Glucocorticosteroids; B1: Non-stricturing, non-penetrating; B2: Structuring; B3: Penetrating.

The incidence of AEs was not associated with prior exposure to IFX; the rates of AEs in IFX-naïve and previously exposed patients were 0.65 (17/26 patients) and 0.53 (7/13 patients), respectively.

Discussion

Not only are data on long-time biologics safety still limited but there is also a tendency towards under-reporting of less severe health problems, such as skin eruptions, fatigue and general malaise.

The most commonly reported side effects of biologic therapy include infections [16] that usually involve upper respiratory tract and urinary tract [17]. While viral infections, such as cytomegalovirus and Epstein-Barr virus infections, have been predominantly linked to frequent IMM therapy, treatment with biologics is typically complicated by opportunistic mycobacterium infections, such as tuberculosis, histoplasmosis, invasive aspergillosis and others [18,19]. The incidence of opportunistic infections in various groups of patients

Table 2: Rates of Adverse Events of Interest. Cumulative rate for both IFX and ADA = 67 events.

	Infliximab	Adalimumab
AE (%)	N=43 (64.17%)	N=24 (35.83%)
Any AE	43	24
Serious AE	0	0
AE leading to discontinuation	3*	0
Infections	9 (10.7)	5 (20.8)
• Upper respiratory tract infections	4 (44.4)	0 (0.0)
• Lower respiratory tract infections	2 (22.2)	2 (40.0)
• Gastro-intestinal infections	1 (11.1)	3 (60.0)
Opportunistic infection	1 (2.3)	0 (0.0)
• oral candidiasis	1 (1.0)	0 (0.0)
Hematologic AE	23 (53.5)	11(24.9)
• Anaemia: 17	17 (73.9)	9 (81.8)
• Leucopenia: 5	5 (21.7)	2 (18.2)
• neutropenia: 1	1 (4.4)	0 (0.0)
Injection site reactions	8 (18.6)	1 (4.2)
• Anaphylactic shock: 3	3 (37.5)	0 (0.0)
• Other Infusion reactions:	3 (37.5)	1(100)
• Urtricaria	2 (25.0)	0 (0.0)
Other	3 (6.9)	2 (8.3)
• Elevated transaminases	1(33.3)	1(50.0)
• Lymphadenopathy	1(33.3)	0 (0.0)
• Positive Tuberculin Test	1(33.3)	0 (0.0)
• Fever	0 (0.0)	1 (50.0)

*Due to Anaphylactic shock switching to ADA.

treated with IFX varies between 0.3% and 0.9%p [20], and seems to be mainly associated with the use of concomitant treatment with either corticosteroids or azathioprine (AZA)/6-mercaptopurine [21]. However, the combination of a biologic with IMM did not increase the risk significantly. In on our analysis, infections turned out to be the second most common AE for both IFX (n=9) and ADA (n=5). Upper respiratory tract infections were the most frequently observed in IFX-treated patients, whereas gastrointestinal infections prevailed among ADA-treated individuals. An opportunistic infection, namely oral candidiasis, was recorded in only one patient treated concomitantly with IFX and AZA; no infections were documented among the patients being on concomitant ADA and IMM treatment.

Anemia was the most common hematologic AE in our series which is consistent with the data published by other authors [22]. It was also the most frequently reported AE overall. However, most of patients presenting with anemia or other hematologic AEs (e.g. leucopenia) received concomitant treatment with IMM or corticosteroid. Therefore, the episodes of anemia could be associated with the use of the concomitant medication, rather than with the biological therapy. Moreover, it should be remembered that one third of IBD patients suffer from recurrent iron deficiency anemia [23], which could also contribute to high incidence of this hematologic disorder documented in our analysis.

The incidence of various post-IFX infusion reactions, such as a burning sensation, itching, erythema and pain, is estimated at 6.1%, [24] and the incidence of serious adverse reactions, e.g. shortness of breath, hypotension or stridor, at 1.0%. However, a genuine allergic reaction is rarely characterized by shortness of breath and urticaria [24]. A total of 8 (7.27%) infusion reactions were documented in our series of 110 patients, which corresponds to similar incidence as previously reported. Three patients developed anaphylactic shock during infusion of IFX; the infusion was stopped and the treatment was switched to ADA in all these cases. The other reactions observed in our patients were mild and could be effectively treated with a single-dose of hydrocortisone; most subjects were re-challenged after the appropriate precautions.

The problem of malignancies concerns mostly internal medicine gastroenterologists because the process of carcinogenesis needs time. A systematic review by Dulai et al. performed to quantify the incidence of serious infection, lymphoma, and death among pediatric patients with IBD who received anti-TNF therapy has demonstrated no greater risk of lymphoma among children with IBD who received anti-TNF therapy comparing to those treated with other IBD therapies or adults treated with anti-TNF agents [25]. We also have not reported any case of cancer nor lymphoma in our patients treated with anti-TNF agents. Nonetheless, we are aware of losing our patients to follow-up when they become older and switch to internal disease gastroenterologist. This is the time; they may develop treatment related malignancies due to prolonged use of immune suppressive or biologic agents.

We are entirely aware of certain limitations of our study, such as its retrospective nature, due to which AEs could be easily missed or not reported by either physician or patient. However, all our patients, in order to get expensive biologic therapy were included into the therapeutic program of Polish National Health Fund (NHF), and thus we were obliged by its protocol to close monitoring and reporting safety issues of the therapy. Therefore, we assume our data decent and fairly reliable.

No serious AEs were observed in the course of biologic therapy, which can be considered as great success. Our experiences suggest that appropriate qualification to biologic treatment, based on a complete evaluation (including a chest X-ray and tuberculin test) and careful monitoring of potential AEs, constitutes the best way of preventing serious complications.

Conclusion

Biologic therapy with IFX and/or ADA is generally well-tolerated and safe, and does not carry a risk of serious AEs. Nevertheless, the patients should be monitored carefully for potential AEs as severe side effects have been reported by other authors.

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