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Research Article

The Use of Concomitant Immunomodulators with Adalimumab Therapy in Pediatric Crohn's Disease

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Abstract

Objectives: Adalimumab is an effective treatment for Crohn's disease but antibody development may cause loss of response. Concomitant use of an immunomodulator reduces the development of antibodies. We performed a 5-year cross-sectional study of variation in use of adalimumab and concomitant therapy in a large pediatric population.

Methods: We identified patients with Crohn's disesae aged <18 years in the Improve Care Now registry who received adalimumab between June 2010 through May 2015, and determined the rates of treatment with adalimumab and concomitant therapy with thiopurine or methotrexate, including variation by age, sex, geographical region and annual change. Chi-square tests compared percentages and the Cochran Armitage Trend Test tested percentages over time and across age groups.

Results: Of 7,271 patients, adalimumab treatment occurred in 1,009 (14%), more likely with increasing age ($p<0.001$), in females ($p<0.001$), and in the West than the Northeast US ($p<0.001$). From year 1 to year 5, the use of adalimumab increased from 7% to 13% ($p<0.001$) and concomitant therapy increased from 25% to 47% ($p<0.001$). Of patients treated with adalimumab, 47% received concomitant therapy with thiopourine (19%) or methotrexate (28%). Concomitant therapy occurred more commonly in younger patients ($p<0.01$) but frequencies by sex were not significantly different ($p=0.17$).

Conclusions: In pediatric Crohn's disease there is increasing use of both adalimumab and concomitant therapy, including both thiopurine and methotrexate, with significant variation by age, sex and region of the US. Further study is needed to determine the effectiveness of and indications for concomitant therapy with adalimumab treatment.

ABBREVIATIONS

CD: Crohn's Disease; TNF: Tumor Necrosis Factor; ADA: Adalimumab; TP: Thiopurine; MTX: Methotrexate; IBD: Inflammatory Bowel Disease

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract that can occur at any age, but typically begins in adolescence and young adulthood. Substantial therapeutic advances have been made in recent years, including the use of biologic drugs, specifically those that block the cytokine, tumor necrosis factor (TNF) [1]. Adalimumab (ADA) is one of several agents that block TNF and has proven to be an effective agent in inducing and maintaining remission in adult patients [2] and has also been shown to be safe and effective in children [3]. The FDA approved ADA for the treatment of adults with Crohn's disease in 2007 but it was not until 2014 that it was approved for pediatric Crohn's disease patient's age 4 years and older.

Expert opinion regarding the use of combination immunodulator and anti-TNF therapy continues to evolve as

evidence further defines the benefits and risks of a combination strategy. The SONIC study of Crohn's adult patients naive to both thiopurine (TP) and infliximab demonstrated the superior efficacy of combination azathioprine and infliximab compared to either medication used alone [4]. The rationale for using an immunomodulator in conjunction with anti-TNF therapy is to limit antibody formation to the anti-TNF, which presumably is one of the major mechanisms for loss of response4. However, definitive data are lacking for other anti-TNF therapies. Additionally, the benefit of continuing immunomodulator therapy in patients who are failing treatment and ready to initiate a biologic has not been studied prospectively. Post-hoc analyses from anti-TNF pivotal trials, as well as retrospective population studies have demonstrated similar efficacy in sub-group analyses of patients treated with monotherapy versus combination therapy [5-7].

Although the topic continues to be highly debated, no real consensus has been reached. The recent ECCO/ESPGHAN Consensus Guidelines on the medical management of pediatric Crohn's disease state that there is insufficient evidence to define the risk/benefit ratio for monotherapy or concomitant therapy in all CD children. However, the point is made that combination therapy in the first six months may be associated with less frequent development of antibodies and subsequent loss of response [8]. Similarly, the American Gastroenterological Association guidelines on agents for the induction and maintenance of remission in adult Crohn's disease includes a statement of no recommendation for or against combination anti-TNF and TP therapy for maintenance of remission in Crohn's disease; however, combination TP therapy with infliximab is recommended for induction of remission [9].

There is an absence of real world data examining the use of combination anti-TNF and TP therapy in pediatric Crohn's disease. In the IMAgINE 1 study of ADA in pediatric Crohn's disease, 62% of patients were taking concomitant immunomodulators at study entry [3], while in the RESEAT retrospective analysis of ADA use in pediatric Crohn's, 41% and 23% of patients were receiving TP and methotrexate (MTX) respectively at the time of initiation of ADA10. In the REACH study of infliximab, over 90% of children entered the study on immunodulator therapy [10,11].

Improve Care Now is a multi-center registry started a decade ago with the main mission to improve quality of care for pediatric patients. We performed a cross-sectional descriptive study to determine the variation in use of ADA and concomitant therapy with either a TP or MTX over a five year period from June, 2010 through May, 2015 in a large population of pediatric Crohn's disease patients in the Improve Care Now registry. Our primary aim was to examine variation by age, sex, type of immunomodulator and region of the US as well as changes in these variables over the last 5 years. Our secondary aim was to explore the feasability of using a large multi-center registry to address this and similar questions. Determination of variation in care is important to understand and optimize the use of ADA and immunomodulators.

MATERIALS AND METHODS

A cross-sectional analysis of children with Crohn's disease less than 18 years of age enrolled in the Improve Care Now Network registry from June 1, 2010 to May 31, 2015 was undertaken. Improve Care Now is a growing multi-center learning health network of clinicians, researchers, patients and parents collaborating to accelerate discovery and innovation and improve the health, care and cost of children and youth with inflammatory bowel disease (IBD). Initiated in 2007 [12], Improve Care Now currently has 95 participating pediatric care centers, including university, multi-specialty group and private practices with 27,000 IBD patients. The Improve Care Now registry currently contains data from 30,000 patients and 185,000 visits. Included in the study cohort were those patients for whom consent was obtained to participate in human subject's research as well as patients who were less than 18 years of age during the calendar year examined. The proportion of patients on ADA was determined as well as the use of concomitant therapy with either a TP or MTX. Concomitant therapy was defined as taking ADA and either TP or MTX at the time of an outpatient visit. Additionally, the number of subsequent visits on concomitant immunomodulators was determined. The variation by age, sex, geographical region, and the annual change in the last five years was determined. Age was categorized as 0 – 5 years, 6 – 10 years, 11 – 14 years, and 15 – 17 years. Centers were grouped by size to see if large centers were contributing a disproportionate number of patients for a particular therapy. Regions of the US were designated as Northeast, South, Midwest and West. A year was defined as from June 1 of the given year to May 31 of the following year. Chi-square tests were used to compare percentages and the Cochran Armitage Trend Test was used to test percentages over time and age groups. Pairwise comparisons for comparing regions were conducted using generalized linear mixed effects models with the binomial distributions and the logit link and the Tukey-Kramer adjustment for multiple comparisons. P-values <0.05 were considered significant. All data manipulations and calculations were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS AND DISCUSSION

During the five year period, 7,271 consented patients with Crohn's disease less than 18 years of age were identified, of whom 1,009 or 14% received ADA. Of the patients receiving ADA over the five year period, 47% had concomitant therapy with either a TP (19%) or MTX (28%). Of patients on concomitant therapy with methotrexate, 68% had two or more visits and for concomitant therapy with a thiopurine, 61% had two or more visits documented in the registry.

ADA was more commonly used with increasing age, with 5% of patients having received the drug between 0 - 5 years of age, 8% of patients between 6 to 10 years of age, 14% of patients between 11 - 14 years of age, and 16% between 15 to 17 years of age ($p<0.001$ for ages 0 - 5 years vs 15 - 17 years) (Table 1). The use of concomitant therapy was most common among the youngest patients (63% of the 0 - 5 year olds), decreasing to 43% of the 15 - 17 year olds ($p=0.001$) (Figure 1). Although the use of a TP did not differ significantly by age ($p=0.68$), MTX use significantly decreased with age from 38% to 24% ($p=0.046$).

ADA was used in 16% of all females compared to 13% of all males ($p<0.001$) (Table 1). There was no significant difference in overall use of concomitant therapy by sex ($p=0.17$) (Figure

Table 1: Proportion of patients receiving concomitant therapy by category (age group, gender, region, and year)

Category	Age Group	Total patients	Patients on Adalimumab (%)	Patients on Adalimumab concomitant therapy (%)	Patients on Adalimumab with thiopurine (%)	Patients on Adalimumab with methotrexate (%)
Age Group* (years)	0 to 5	163	8 (5%)	63%	25%	38%
	6 to 10	1112	88 (8%)	59%	24%	35%
	11 to 14	2898	417 (14%)	49%	19%	31%
	15 to 17	3073	495 (16%)	43%	19%	24%
	Overall	*7271*	*1009*	*47%*	*19%*	*28%*
	p-value		*< 0.0001*	*0.01*	*0.68*	*0.046*
Gender#	Male	4247	542 (13%)	49%	15%	34%
	Female	2998	465 (16%)	§44%	25%	20%
	*Overall	*7271*	*1009 (14%)*	*47%*	*19%*	*28%*
	p-value		*0.0009*	*0.17*	*< 0.0001*	*< 0.0001*
Region of Country	Northeast	1314	139 (11%)	38%	20%	18%
	South	2887	415 (14%)	43%	14%	28%
	Midwest	2346	330 (14%)	54%	23%	31%
	West	724	125 (17%)	54%	24%	30%
	Overall	*7271*	*1009* (14%)	*47%*	*19%*	*28%*
	p-value		*0.0002*	*0.01*	*0.0008*	*0.01*
Year of Study	2010-2011	88	7%	25%	11%	14%
	2011-2012	183	9%	27%	13%	15%
	2012-2013	290	9%	36%	16%	21%
	2013-2014	448	11%	45%	15%	30%
	2014-2015	682	13%	48%	19%	30%
	p-value		*< 0.0001*	*< 0.0001*	*0.01*	*< 0.0001*

**25 patients missing age, of which 1 was on adalimumab*
#26 patients missing gender, of which 2 were on adalimumab
§ *Rounding of percentages alter the total*

1); however, there was a significant difference with regard to specific immunomodulator, as 15% of males received a TP and 34% received MTX, whereas 25% of females received a TP and 20% received MTX (p<0.0001).

ADA treatment was lowest in the Northeast (11%) compared to 14% of patients in both the South and Midwest, and 17% in the West (p<0.0002 for Northeast vs West) (Table 1). Concomitant therapy occurred less frequently in the Northeast than in the other regions (p=0.01). There was also significant variation by region in the use of TP (p=0.008) and MTX (p=0.01). Center size did not influence the variability of use of concomitant therapy.

The proportion of patients on ADA increased in each year, from 7% in 2010-2011 to 13% in 2014-2015 (p< 0.0001) (Table 1). Concomitant therapy increased each year with 25% in 2010-2011 and 49% in 2014-2015 (p<0.0001) (Figure 2). Specifically, TP use increased from 11% in 2010-2011 to 19% in 2014-2015 (p=0.01) while MTX use increased from 14% in 2010-2011 to 30% in 2014-2015 (p<0.0001). The overall use of ADA among the entire population of Crohn's patients rose from 7% in 2010-2011 to 13% in 2014-2015, while ADA and concomitant use rose from 2% to 6% during the same period (Figure 3).

The Improve Care Now registry was used to identify over 1,000 pediatric Crohn's patients less than 18 years of age who have received ADA over a 5-year period ending in May, 2015. This represents 14 % of patients with Crohn's disease in the registry during this time period. Of those patients receiving ADA, 47% received concomitant therapy with an immunomodulator, either TP or MTX. There was significant variation in the use of ADA: use was more common in older patients, females and in the West compared to the Northeast of the United States. Also the use of ADA nearly doubled over the five-year period. Similarly there was significant variation in the use of concomitant therapy: use was more common in younger patients and in the Midwest and West, but did not vary significantly by sex; proportional use of concomitant therapy also nearly doubled over the five-year period. The use of TP did not vary significantly by age, but was more common among females, more common in the Midwest and West; proportional use nearly doubled over the five-year period. The use of MTX was more common in younger patients, males and in the Midwest and West; proportional use doubled over the five-year period.

Currently, there is debate about the use of TP either as monotherapy or concomitant therapy in pediatrics due to a

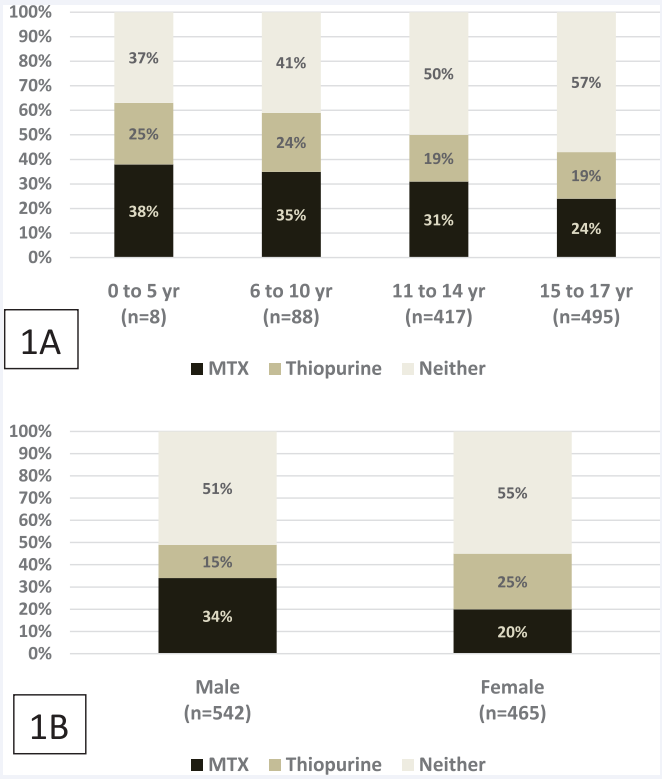

Figure 1 Adalimumab therapy concomitant with MTX or thiopurine or monotherapy based on age, B: Adalimumab therapy concomitant with MTX or thiopurine or monotherapy based on gender.

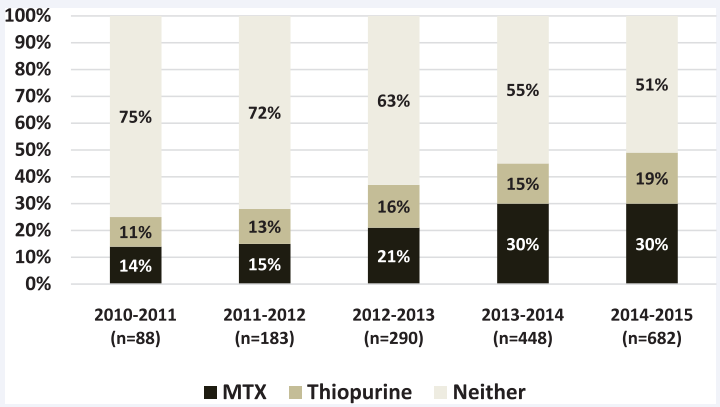

Figure 2 Adalimumab therapy concomitant with MTX or thiopurine or monotherapy based on calendar year.

concern for potential malignancy, particularly hepatosplenic T-cell lymphoma, which is more prevalent in 15 to 30 year old males [13]. A multicenter pediatric study identified 502 patients on infliximab therapy and showed that approximately 40% of patients were on concomitant immunomodulators and was able to remain on infliximab for a longer period of time [14].

It is not clear why there was increased use of ADA as children got older in our study; it may be due to many patients having been previously treated for some time with infliximab. Of note, concomitant therapy was more often utilized in the younger age groups, perhaps consistent with the generally held tenet that younger children have more severe disease and warrant more aggressive therapy15. ADA while thought to have less immunogenicity than IFX, still has been to have significant incidence of antibody formation In addition, older children may prefer ADA over IFX due to lack of interruption of daily activities that infusion incurs, as well as preference when attending university to minimize missed class time due to infusions.

There seemed to be a higher proportion of use of ADA in the West, followed by the South and the Midwest, and the least in the Northeast. Interestingly the use of concomitant therapy by region also paralleled ADA therapy overall, even after adjusting for differences in age and sex. Reasons for these regional differences are unknown.

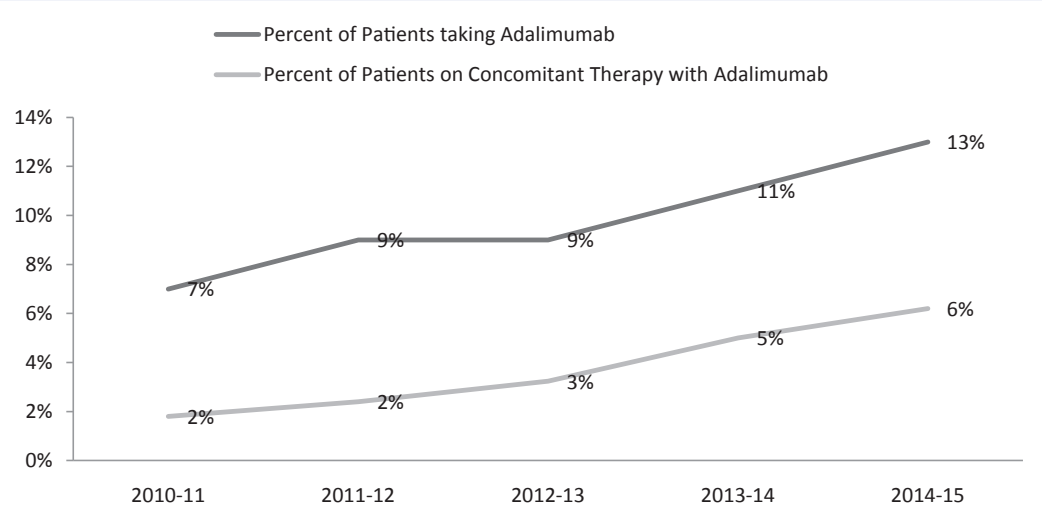

Figure 3 Percent of total patients per year on adalimumab monotherapy or concomitant therapy.

One limitation of a retrospective study is the potential for selection or information bias; however, in the current study the large number of centers and clinicians would tend to mitigate these potential biases. Another limitation of this study is that patients who did not give consent for human subject's research were not included in the analyses. However, over 75% of patients in the Improve Care Now registry for more than one year have given such consent. Improve Care Now centers register over 80% of their patients, who are diverse in age, ethnicity, race and income. Nonetheless, it is not known how representative this study population is. In addition, even though Improve Care Now currently had 95 participating centers at the time, it is not known if there is regional variation in participation.

We did not analyze disease characteristics or outcomes, as it was beyond the scope of the study. Disease phenotype, for example, may have been a factor in choosing monotherapy or concomitant therapy. Another limitation is that we were unable to determine the precise duration of concomitant therapy for some patients. A long term cost analysis would have been very interesting well but beyond the scope of the study. For most of the study, ADA was not FDA approved for pediatric Crohn's disease. Evaluation of the utilization of other biologics as well as the sequence was beyond the scope of this project but is currently being studied by other Improve Care Now investigators.

CONCLUSION

By examining a large population of children and adolescents with Crohn's disease, we have been able to demonstrate the frequency and characteristics of a relatively new pediatric therapeutic agent and, more importantly, how frequently it is being used with concomitant therapy. Further study is needed to determine the effectiveness of and indications for concomitant immunomodulator therapy with ADA treatment.

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CONFLICT OF INTEREST

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