**Name of Journal: *World Journal of Gastroenterology***

**Manuscript NO: 35562**

**Manuscript Type: ORIGINAL ARTICLE**

***Retrospective Study***

**Efficacy of thalidomide therapy in pediatric Crohn’s disease with evidence of tuberculosis**

Wang L *et al*. Thalidomide in pediatric CD with tuberculosis

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**Author contributions:** Wang L, Hong Y and Wu J collected the data; Wang L analyzed the data and drafted the manuscript; Huang Y and Leung YK designed and supervised this study; all authors approved the final version to be published.

**supported by** Medical Science and Technology Planning Project of Zhejiang Province, China, No. 2015KYB430 (to Hong Y).

**Institutional review board statement:** The study was approved by the ethics committee of Children’s Hospital of Fudan University, Shanghai, China.

**Informed consent statement:** All the patients and/or their legal guardians provided written consent forms for the study.

**Conflict-of-interest statement:** All the authors listed here declare no conflicts of interest related to this study.

**Data sharing statement:** The dataset is available from the corresponding author at yhuang815@163.com.

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**Manuscript source:** Unsolicited manuscript

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**Received:** July 26, 2017

**Peer-review started:** July 26, 2017

**First decision:** August 10, 2017

**Revised:** August 28, 2017

**Accepted:** September 13, 2017

**Article in press:**

**Published online:**

**Abstract**

***AIM***

To evaluate the efficacy of thalidomide for treating troublesome cases in pediatric Crohn’s disease (CD) with tuberculosis infection.

***METHODS***

A retrospective study of clinical outcome among children treated with thalidomide was conducted. All patients had evidence of tuberculosis infection with a failure of anti-tuberculosis treatment for more than one year, and were subsequently diagnosed with CD. All the patients were applied thalidomide treatment with a starting dose of 1.2-2.5 mg/kg·d. Remission was defined as pediatric CD activity index less than or equal to 10.

***RESULTS***

Ten patients with CD were treated with thalidomide at an average age of 7.2 years and followed up for a median of 22.2 mo. Clinical remission was 60% after 9-12 mo of thalidomide treatment. One patient with no response had an interleukin-10 receptor alpha gene mutation. Erythrocyte sedimentation rate, C-reactive protein and platelet count showed a dramatic decrease; hemoglobin level and weight improved significantly after thalidomide treatment when compared with the baseline values.

***CONCLUSION***

Thalidomide is an effective and safe drug in inducing remission for pediatric patients with CD who have been treated for tuberculosis.

**Key words:** Thalidomide; Children; Inflammatory bowel disease; Intestinal tuberculosis; Anti- tubercular treatment

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**Core tip:** Therapy for Crohn’s disease (CD) and intestinal tuberculosis are totally different, and anti-TNF alpha treatment may increase the risk of tuberculosis reactivation. That makes it still tough to treat patients with severe CD concomitant tuberculosis, especially in high tuberculosis prevalence areas. In the current study, all patients had evidence of tuberculosis infection and diagnosed with CD. Thalidomide showed a positive result for those special cases, and it could be an alternative drug after treatment of tuberculosis has been completed.

Wang L, Hong Y, Wu J, Leung YK, Huang Y. Efficacy of thalidomide therapy in pediatric Crohn’s disease with evidence of tuberculosis. *World J Gastroenterol* 2017; In press

**INTRODUCTION**

Crohn’s disease (CD) is a chronic inflammatory disorder affecting an increasing number of patients each year around the world[1]. It is characterized by abdominal pain, diarrhea, bloody stool and other extra-intestinal manifestations, also impacts on growth in children and adolescents. Wang *et al*[2] reported a multicenter retrospective study from China which revealed childhood-onset inflammatory bowel disease as an emerging disease with a 12-fold increase of incidence over the past decade. Intestinal tuberculosis (ITB) shares a close resemblance in clinical, endoscopic and histological manifestations with CD, making the differential diagnosis of these two diseases a difficult task[3]. At the same time, tuberculosis (TB) is and has always been a major public health problem worldwide, especially in the lower income countries[4]. With the changing epidemiology of TB and CD, it is not unusual to encounter the coexistence of these two diseases, especially in highly TB endemic areas[5].

Managing CD with steroids, immunomodulatory therapy and biological agents in high TB prevalence regions is challenging since those treatments are associated with an increased risk of tuberculosis reactivation for active or latent TB[6]. Considering a high incidence of TB in developing countries, empirical anti-tubercular treatment (ATT) is used to differentiate between ITB and CD[7]. However, the use of anti-TB medications may pose a risk of toxicity and cause unnecessary delay for management of CD patients.

 In 2011, our pilot study reported our experience that three pediatric patients with CD that concomitant with tuberculosis achieved clinical remission after six months of thalidomide therapy[8]. Similarly, a later case report presented an adult patient with CD and pulmonary TB who was steroid-dependent and unresponsive to infliximab, but he exhibited an excellent response to thalidomide treatment[9]. The current study enrolled 10 pediatric-onset patients who had symptoms and evidence suggestive of CD and tuberculosis; we aimed to evaluate the efficacy of thalidomide on clinical remission of all cases in long term follow-up.

**MATERIALS AND METHODS**

***Patients***

This is a tertiary medical center, retrospective study of pediatric CD patients (age < 18 years) with tuberculosis treated with thalidomide at Children’s Hospital of Fudan University from July 2009 to April 2016. Tuberculosis diagnosis was established based on at least one of the following criteria: (1) histological demonstration of acid fast bacilli (AFB) in intestinal tissues; (2) positive TB culture; and (3) positive tuberculin skin testing. All of the patients received a full course of anti-TB medications prior to thalidomide administration. The diagnosis of CD was based on endoscopic and clinical symptoms and also defined as no improvement of clinical and endoscopic symptoms after anti-TB treatment for at least one year.

***Treatment***

Thalidomide (manufactured by Changzhou Pharmaceutical Factory, Changzhou, China) was administered orally at a starting dose of 1.2-2.5 mg/kg·d. The decision to modify the dosage was made by the director of gastroenterology department according to the response and disease activity. To minimize adverse events, thalidomide was taken every evening. This study was approved by the Ethics Committee of Children’s Hospital, Fudan University. Written consent was obtained from parents or legal guardians of the patients after they were informed about possible adverse events. Contraception was controlled in the patients who were in reproduction age.

***Outcome***

A retrospective chart review of medical records was performed to collect baseline demographic and disease characteristics, results of clinical indices and adverse events during follow-up. Pediatric CD Activity Index (PCDAI)[10], as primary outcome, was used to evaluate the response to the treatment from the time of thalidomide initiation and at 9-12 mo thereafter. Each patient was served as his/her own historical control. Clinical remission was defined by PCDAI less than or equal to 10, significant response was a decrease in PCDAI at least 12.5 points from baseline[11]. The clinical indices of erythrocyte sedimentation rate (ESR; normal range 0-20 mm/h), C-reactive protein (CRP; normal range 0-8 mg/L), platelet count and hemoglobin were compared before and after treatment. Weight for age *Z* score by Chinese standardized growth curve was evaluated as a measurement of nutritional index.

***Statistical analysis***

All analysis was performed using SPSS 18.0 (SPSS Inc., Chicago, IL). Quantitative variables were presented as mean ± SD or median with range. Continuous variables were evaluated using paired Student’s *t*-test with normal distribution and Wilcoxon test with non-normal distribution. Statistical significance level was set at two-sided *P* < 0.05.

**RESULTS**

***Baseline characteristics***

Ten pediatric patients treated with thalidomide were identified in the study. There were 6 females and 4 males, with an average age at thalidomide treatment of 7.2 years (range: 2-13.5 years). The mean disease duration before thalidomide therapy was 24 mo (range: 16-42 mo). The average length of follow-up was 22.2 mo (range: 9-44 mo) after the initiation of thalidomide. Clinical characteristics are summarized in Table 1.

All patients have received ATT treatment for more than one year with the average age of 5.3 years (range: 0.2-12.0 years). Seven children were previously treated with HRZ (isoniazide, rifampicin and pyrzinamide) drugs. All patients have evidence of tuberculosis existence; AFB positive was observed in eight cases and positive tuberculin skin testing in two. One patient suffered from spleen TB and cell culture of Mycobacterium was positive. The mean duration of ATT treatment was 18 mo (range: 12-36 mo).

In the present cases, two showed prominently colonic involvement, seven had ileocolonic diseases and the remaining one had isolated ileal disease. Six patients presented with perianal disease, one suffered from joint involvement and one had oral ulcers.

***Outcome***

**Disease activity:** At baseline, seven patients had moderate-to-severe disease activity (PCDAI > 30). There was a significant decrease in the PCDAI score from 37.3 ± 14.1 in the beginning to 16.0 ± 17.9 after 9-12 mo treatment (*P* < 0.05) (Figure 1). Clinical remission was achieved in six patients (60.0%) and there was a response in three cases (30.0%) at 9-12 mo after commencement of thalidomide treatment. For those three patients whose follow-up times were longer than 36 mo, they were still in remission. Case 4 was unresponsive to infliximab prior to positive AFB, but was responsive to thalidomide. In case 2, the PCDAI increased from 52.5 to 60, indicating that she didn’t respond to thalidomide. Given her early-onset symptoms and severe perianal abscess, we performed the whole exome sequencing for case 2 and found a causative interleukin-10 receptor alpha (IL10 RA) mutation. One of the compound heterozygous variants was c.301C>T inherited from her father, and the other was c.537G>A from her mother. She has since been treated with umbilical cord blood transplantation, which was described in our published data[12,13].

Given the lack of complete data, we only evaluated some cases’ response at different points in time. Case 1 showed significant clinical response on the first one month (PCDAI decreased from 45 to 15), case 5 and case 7 attained clinical remission (PCDAI<10) after 2 mo and one month of treatment, respectively. With regard to TB status, the positive AFB findings were turned to negative in case 3 and case 8 after 16 months and 10 months of treatment, respectively.

Overall, the laboratory assessment showed significant drop after thalidomide therapy in ESR (baseline: 26.1 mm/h ± 14.5 mm/h; follow-up: 11.5 mm/h ± 12.0 mm/h) (normal range: 0-20 mm/h) (*P* = 0.037) (Figure 2A), CRP (baseline: 64.0 mg/L ± 46.5 mg/L; follow-up: 25.1 mg/L ± 47.8 mg/L) (normal range: 0-8 mg/L) (*P* = 0.004) (Figure 2B) and platelet (baseline: 471.1 × 109/L ± 178.3 × 109/L; follow-up: 328.4 × 109/L ± 163.8×109/L) (*P* = 0.002) (Figure 2D), with a marked improvement in hemoglobin level (baseline: 111.0 g/L ± 13.4 g/L; follow-up: 119.5 g/L ± 19.7 g/L) (normal range: 110-160 g/L) (*P* = 0.105) (Figure 2C). Weight values at 9~12 months after starting the treatment showed a dramatic increase when compared with the baseline ones (21.03 ± 13.4 *vs* 27.8 ± 19.3) (*P* < 0.05). The changes of weight for age *Z* score are shown in Figure 3.

**Dose escalation:** The majority of patients (70%) were started on an initial dose of 2 mg/kg·d or more. During follow-up, four cases had thalidomide dose increased (to a maximum of 3 mg/kg·d). And the details of dose changes in each individual patient were listed in Table 2. Doses were successfully decreased for all cases after responding to thalidomide. Among all cases, two were discontinued thalidomide administration within follow-up time due to clinical remission and one patient with IL10 RA deficiency stopped due to no response (Table 1). The median cumulative dose for all patients until the end of follow-up time was 16.0 g. For case 5, the cumulative dose was over 28 g. He discontinued thalidomide after 22 mo of treatment, but the symptom of oral ulcers relapsed. However, the patient later opted to restart thalidomide and responded quickly. He was in remission with a minimum dose of 0.5 mg/kg·d. In all cases, 4 of them completely discontinued anti-tuberculous drugs and then given thalidomide treatment, the other 6 patients were continued receiving anti-tuberculous medications. In terms of the treatment for CD, 6 cases were treated with 5-ASA as well as thalidomide, one patient was received nutritional treatment.

Otherwise, no significant relations were seen between the disease duration, disease location or age of diagnosis and remission or response to thalidomide treatment.

***Adverse events***

One patient (case 5) was complained of drowsiness and one (case 1) had dryness in eyes, the symptoms were relieved without reducing dose or discontinuation. One patient (case 8) developed dryness in eyes and knee pain, and then recovered after discontinuation of thalidomide. She subsequently re-administrated thalidomide without any adverse effects occurring. None of these patients presented symptoms and signs of sensory impairment during the follow-up period.

**DISCUSSION**

This study represents an experience with thalidomide for CD who has been treated for tuberculosis in a young age population. We found 60% of patients in our study achieving clinical remission after 9-12 mo of treatment and the measured parameters were significantly improved in most patients.

Previous studies have well described the efficacy of thalidomide in adult-onset CD patients[14-17]. Facchini *et al*[18] first reported five pediatric CD patients were administered with thalidomide as refractory cases or the last medical resort before surgical intervention, 4 of them were in remission after 19-24 mo of treatment. A long-term retrospective study assessed that remission was achieved with thalidomide in 17 of 19 children and adolescent patients with CD and 80% of patients suspended steroids successfully[19]. In a later retrospective series of 12 children with severe refractory CD who failed to respond to infliximab and adalimumab, the results showed 83.3% clinical remission and 71.4% complete fistula closure after using thalidomide as a rescue therapy[20]. In our study, one case (No. 4) also failed to respond to infliximab, but responded to thalidomide therapy. Recently, the first multicenter, double-blind randomized clinical trial provided more information concerning the efficacy and safety of thalidomide on active pediatric CD despite immunosuppressive treatment. In that study, 31 of 49 (63.3%) children achieved clinical remission and 65.3% achieve 75% response after 1.5 to 2.5 mg/kg·d thalidomide treatment[21]. Our findings with 60% remission and 30% response rate are comparable with those studies.

One of the most important features in the current study is that all patients had laboratory findings consistent with infection with tuberculosis. Of note, we found evidence of AFB presence in 80% of patients which indicated tuberculosis infection. Thus, it is reasonable that they were first treated with anti-TB medications, but treatment unfortunately failed despite administration for more than one-year. Given that CD and ITB have marked overlap in clinical, endoscopic and histologic features, CD diagnosis was then determined as the failure of ATT therapy, and majority of our cases had perianal disease which is more common in CD than ITB. While it is undeniable that the two conditions could be coexisted in countries with high TB prevalence, one hypothesis suggests that *Mycobacterium avium* subspecies might be a cause of CD[22]. In 2011, a successful use of thalidomide under such circumstances that patient with CD and also tuberculosis infection has also been reported[9]. In fact, thalidomide has been shown to be effective as an adjuvant treatment for intractable intracranial tuberculosis and another central nervous system tuberculosis infection that didn’t respond to standard medical and surgical therapy[23-25]. It has been postulated that the mechanism of action of thalidomide is associated with inhibiting tumor necrosis factor alpha secretion. It could also co-stimulate T lymphocytes and have a greater effect on CD8+ than CD4+ T cells since CD8+ T cells have a protective immunological effect in Mycobacterium tuberculosis infection[26]. Therefore, as to its positive role in tuberculosis infection, the application of thalidomide seems to be able to avoid the contraindication to use infliximab in patients with latent or active TB and reduce the damage from delaying treatment of CD.

As a sedative and antiemetic agent during pregnancy in the 1950s, thalidomide was withdrawn from the market due to potential teratogenicity. The most commonly encountered adverse effect of thalidomide treatment is the peripheral neuropathy which impedes its long-term use. With regards to safety, our experience showed that drowsiness was the most common adverse reaction to thalidomide. The relationship between peripheral neuropathy and cumulative dose has been investigate in a previous study which pointed that 25% of patients complained of peripheral neuropathy and all were with cumulative doses over 28 g[19]. In our cases, only one reached high cumulative dose within the follow-up periods. The low dose administration may be one of the reasons for no obvious adverse events, or it could be due to the short term follow-up in our study. However, it is noteworthy that one case with a cumulative dose over 28 g encountered disease relapse after thalidomide discontinuation and recovered soon after restarting thalidomide at a very low daily dose, indicative of thalidomide-dependency. Clearly, this still needs further investigation with similar cases.

Our study had some limitations. There was no control group to compare the effect of other medications because the natural course of CD can be spontaneous remission and exacerbation during the process of disease. We selected the self-control study to reduce the bias. Although our study is the largest reported experience with thalidomide in pediatric patients with CD who has been treated for tuberculosis, its retrospective design creates several limitations that are important to note. A prospective study should be set up in the future. We also did not perform *Mycobacterium* culture and electromyography because no patient presented symptoms and signs of sensory impairment.

Based on all results, we would like to conclude thalidomide is an effective and safe drug in inducing clinical remission and improving laboratory parameters for pediatric patients with CD who have been treated for tuberculosis infection. It could be used as an alternative drug after treatment of TB has been completed. A controlled, long-term trial of thalidomide in patients with those conditions awaits further investigation.

**ACKNOWLEDGMENTS:**

We would like to express the gratitude to all the patients and their families for their participation and support of this study.

**COMMENTS**

***Background***

Since Crohn's disease (CD) and tuberculosis (TB) remain global problems, these two conditions could be present in the same patient, especially in high tuberculosis endemic areas. However, biological agents or immunosuppressive drugs, as effective medications for CD, may increase the risk of tuberculosis reactivation. Therefore, it is urgent to develop a suitable therapy for those troublesome cases in CD with tuberculosis infection.

***Research frontiers***

Anti-TNF alpha treatment may increase the risk of tuberculosis reactivation. This makes it difficult to treat severe inflammatory bowel disease patients in high endemic area for tuberculosis. Thalidomide is reported to be effective in pediatric CD, and it is also safe for treatment of intracranial tuberculosis as an adjuvant therapy.

***Innovations and breakthroughs***

The authors describe a small series of 10 pediatric patients with evidence of tuberculosis. Following at least one year of anti-tubercular therapy, patients were started on thalidomide due to persistence of gastrointestinal symptoms and endoscopic abnormalities consistent with CD. Clinical remission was reached to 60% after 9-12 mo of thalidomide treatment. Importantly, no exacerbation of TB was reported during a mean follow-up period of 22.2 mo. The results of the study may be relevant for clinicians dealing with CD in countries with high prevalence of tuberculosis.

***Applications***

This is a retrospective case series of 10 pediatric CD complicated with coexisted tuberculosis from one institution. In TB prevalent region where CD is also prevalent, the potential benefit using thalidomide provides a reasonable option.

***Terminology***

Anti-tubercular treatment refers to the use of response to the therapy to differentiate between tuberculosis and CD. PCDAI means Pediatric CD Activity Index, a scale to assess the severity of the disease.

***Peer-review***

This study presented a retrospective experience with thalidomide to treat children with CD who had laboratory evidence of infection from Mycobacterium Tuberculosis. The patient numbers included in this study are small. However, it is clinical research and it provides useful information for the management of pediatric CD.

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**P-Reviewer:** Tommasini a, Zhang l, Lakatos PL **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** China

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C, C

Grade D (Fair): 0

Grade E (Poor): 0



**Figure 1 Changes in pediatric Crohn’s disease activity index before and after 9-12 mo of thalidomide treatment that performed on 10 patients.** There was a decrease of the pediatric CD activity index (PCDAI) scores in nine patients (*P* < 0.05), 6 of them achieved clinical remission (PCDAI < 10). PCDAI: pediatric Crohn’s disease activity index.



**Figure 2** **Changes of laboratory indices before and after 9-12 mo treatment in 10 Crohn’s disease patients with tuberculosis.** A. Erythrocyte sedimentation rate (ESR); B: C-reactive protein (CRP); C: Hemoglobin (Hb); D: Platelet (PLT). It showed significant reductions in ESR, CRP and platelet levels (*P* < 0.05); and an increasing trend in Hb levels.



**Figure 3 Changes weight for age *Z* score before and after 9-12 mo treatment in 10 cases treated with thalidomide.**

**Table 1 Clinical characteristics of all cases treated with thalidomide**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient No.** | **Sex** | **Age of thalidomide treatment** | **Disease duration before thalidomide**  | **Age of ATT treatment**  | **Disease distribution** | **Extra-intestinal symptoms** | **TB status before ATT** | **ATTmedications and duration** | **Thalidomide start dose** | **Thalidomide final dose****(duration)** | **Follow-up time (mo)** | **Response**  |
| 1 | M | 2 yr 8 mo | 26 mo | 1 yr 3 mo | Ileocolonic  | Joint lesions | AFB(+), PPD(+) | HRZ, 6m;HRZEP, 6 mo | 2.5 mg/kg·d | - (34m) | 38 mo | Remission  |
| 2 | F | 2y | 23 mo | 2 mo | Colon  | Perianal abscess | AFB(+) | HRZ, 3 mo;HR, 15 mo | 2.5 mg/kg·d | - (7m) | 10 mo | No response |
| 3 | F | 2 yr 4 mo | 28 mo | 7 mo | Colon  | Perianal abscess | AFB(+) | HRZ, 9 mo;HREP, 27 mo | 2 mg/kg·d | 0.33 mg/kg·d | 33 mo | Response  |
| 4 | F | 11 yr 7 mo | 42 mo | 8 yr 1 mo | Ileocolonic | Perianal skin tag | AFB(+) | HREZ, 12 mo | 1.8 mg/kg·d | 0.8 mg/kg·d | 15 mo | Response  |
| 5 | M | 12 yr 6 mo | 18 mo | 11 yr 3 mo | Ileocolonic | Oral ulcers | TB culture (+),Spleen TB | HRS, 5 mo;HRE, 12 mo | 2 mg/kg·d | 0.5 mg/kg·d | 36 mo | Remission |
| 6 | M | 12 yr 5 mo | 20 mo | 11 yr 5 mo | Ileocolonic | Anal fistula  | AFB(+) | HRZ, 12 mo | 1.2 mg/kg·d | 0.6 mg/kg·d | 12 mo | Remission |
| 7 | M | 8 yr 6 mo | 38 mo | 5 yr 4 mo | Ileal  | Pleural and ascetic fluid | PPD(+) | HRE, 3 mo;HRZ, 12 mo | 2 mg/kg·d | - (44m) | 44 mo | Remission |
| 8 | F | 3 yr 8 mo | 16 mo | 2 yr 4 mo | Ileocolonic | - | AFB(+) | HRZ, 14 mo;HRE, 12 mo | 2 mg/kg·d | 1.6 mg/kg·d | 16 mo | Response |
| 9 | F | 2 yr 4 mo | 16 mo | 1 yr  | Ileocolonic | Anal fissure  | AFB(+) | HRZ, 14 mo | 2.2 mg/kg·d | 1.8 mg/kg·d | 9 mo | Remission |
| 10 | F | 13 yr 6 mo  | 17 mo | 12 yr 1 mo  | Ileocolonic | Perianal skin tag | AFB(+) | HREZ, 3 mo;HR, 15 mo | 1.8 mg/kg·d | 1.3 mg/kg·d | 9 mo | Remission |

ATT: Anti-tubercular treatment; H: Isoniazid; R: Rifampicin; Z: Pyrazinamide; E: Ethambutol; S: Streptomycin; P: para-aminosalicylic acid.

**Table 2 Available data for the dose changes at different time-points after thalidomide treatment**

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| **Patient No.** | **Dose (mg/kg·d) at different follow-up time (mo)** |
| 1 | 2.5 (baseline) - 2.5 (1 mo) - 1.2 (12 mo) - stop (34 mo)  |
| 2 | 2.5 (baseline) - stop (7 mo) |
| 3 | 2 (baseline) - 1.1 (12 mo) - 0.7(18 mo) - 0.4 (21 mo) - 0.33 (33 mo) |
| 4 | 1.8 (baseline) - 3 (5 mo) - 1 (12 mo) - 0.8 (15 mo) |
| 5 | 2 (baseline) - 0.5 (2 mo) - 1.8(9 mo) - stop (22 mo) - 0.5 (36 mo) |
| 6 | 1.2 (baseline) - 0.6 (12 mo) |
| 7 | 2 (baseline) - 1.8 (1 mo) - 1.1 (10 mo) – stop (44 mo) |
| 8 | 2 (baseline) – 2.4 (10 mo) - 1.6 (16 mo) |
| 9 | 2.2 (baseline) -1.4 (5 mo) - 1.8 (9 mo) |
| 10 | 1.8 (baseline) -1.3 (9 mo) |