

# Golimumab in adolescents with Crohn's disease refractory to previous tumor necrosis factor antibody

Judith Pichler (✉ [judith.pichler@meduniwien.ac.at](mailto:judith.pichler@meduniwien.ac.at))

University Children Hospital Vienna

**Nima Memaran**

Hochschule Hannover

**Wolf-Dietrich Huber**

University Children Hospital Vienna

**Christoph Aufricht**

University Children Hospital Vienna

**Bettina Bidmon-Fliegenschnee**

University Children Hospital Vienna

---

## Research article

**Keywords:** Crohn's disease, golimumab, clinical response, adolescents

**Posted Date:** January 17th, 2020

**DOI:** <https://doi.org/10.21203/rs.2.21120/v1>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

**Version of Record:** A version of this preprint was published at Acta Paediatrica on September 30th, 2020.

See the published version at <https://doi.org/10.1111/apa.15522>.

# Abstract

**Background** Inducing and maintaining clinical remission in children with Crohn's disease (CD) is associated with treatment with antibody to tumor necrosis factor (TNF)- $\alpha$  such as infliximab or adalimumab. In the treatment of paediatric CD, there are no data about the use of a third introduced subcutaneous TNF-antibody, golimumab,

**Methods** We evaluated the efficacy of golimumab for adolescents with moderate/severe CD. Retrospective analyses were done in all 7 (5 girls) adolescents who received golimumab at a median age of 17 years for a median of 7.2 months. Paediatric Crohn's disease activity index (PCDAI), full blood count, inflammatory markers, use of corticosteroids and adverse events were recorded.

**Results** With golimumab, 5 of the 7 children were PCDAI responders and 2 entered remission (PCDAI<10). There was a significant increase in haematocrit after 2 weeks, faecal calprotectin was significantly reduced after 4 weeks compared to baseline. Out of five children, steroid withdrawal was possible in one and steroid reduction in two cases. There were no serious side effects.

**Conclusion** With moderate/severe CD, golimumab induced and maintained clinical response. The majority of children were PCDAI responders, in most steroid sparing was possible. Golimumab might be an effective rescue therapy in refractory CD.

## Background

Crohn's disease (CD) is an immune-mediated disorder resulting in chronic relapsing inflammation of the gastrointestinal tract [1]. In paediatric CD, enteral nutrition as induction therapy is as safe and effective as prednisolone [1,2]. As maintenance therapy, the start of immunomodulators such as methotrexate, azathioprine or 6-mercaptopurine is effective, especially in steroid dependent children [1,3].

In refractory IBD, treatment failures of immunomodulators and steroids helped to the development a new class of drugs such as biologicals. Most biologicals used for CD target the proinflammatory cytokine tumor necrosis factor (TNF)- $\alpha$ , since dysregulation of TNF- $\alpha$  plays an important role in CD [1,4]. The number of TNF- $\alpha$  producing cells is greatly increased in the intestinal mucosa and lumen of patients with CD and increased concentrations of TNF- $\alpha$  have been found in the stool of children with CD [1,4-7].

The monoclonal chimeric anti TNF- $\alpha$  antibody Infliximab (IFX, Remicade<sup>®</sup>, Merck Sharp & Dohme Corp, Whitehouse Station, NJ, USA) [8-11] and the fully human anti TNF- $\alpha$  antibody, Adalimumab (ADA, Humira<sup>®</sup>, Abbott Laboratories, North Chicago, Illinois, USA) [11-14] have been proven to be effective therapies for paediatric patients with moderate-to-severe CD. Concerns regarding loss of IFX and ADA effect have led to the release of an additional fully human monoclonal anti-TNF- $\alpha$  antibody Golimumab (GLM, Simponi<sup>®</sup>, Janssen Biotech, Inc., Horsham, PA, USA) [11,15]. GLM has been shown to be efficacious in the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis in adults [16-21] and furthermore was approved in 2013 for the treatment of adult patients with moderate and

severe active ulcerative colitis (UC) [22,23]. There is only one abstract about the use in CD in adults, where Ben-Bassat et al. evaluated the efficacy of GLM in nine patients with moderate to severe CD who failed other anti-TNF- $\alpha$  treatment [24].

GLM is currently not licensed for the use in paediatric inflammatory bowel disease (IBD) patients, however a recent international multicentre study in 35 children aged 6-17 years with UC naïve to any TNF- $\alpha$  antibody showed at week 6 54% mucosal healing with no clinically important safety concerns [11,25-27].

To our knowledge, there is scant literature for GLM in the use of paediatric CD, so the efficacy of GLM for the induction of remission in paediatric CD patients is still unknown [28]. There is only one paediatric study that describes the use of GLM in 6 adolescents with severe paediatric CD onset. After introduction of treatment, the levels of inflammatory markers declined, however, the clinical response could not be sustained [28].

The aim of this study was to report our experience in the usage of GLM in a small cohort of paediatric patients with CD. We report the clinical effect, efficacy and safety of GLM in children refractory to previous treatment with IFX and ADA.

## **Methods**

### **Study design**

This retrospective case series was performed at a tertiary care paediatric centre. Seven paediatric patients receiving GLM between May 2012 and April 2014 were identified and their medical records reviewed. The indication in all cases for GLM was severe CD, refractory or intolerant to previous treatment including IFX and ADA. The diagnosis for CD was made using standard criteria [29,30] and classified using Paris Classification for CD [31].

### **Golimumab**

All patients were started on subcutaneous GLM therapy with an induction therapy administration every other week followed by maintenance therapy with monthly administration. A total of 4 patients were administered 200mg, then 100 mg 2 weeks later for induction and 50mg as maintenance. Two received induction dose and maintenance dose of 100mg and one child induction dose and maintenance doses of 50mg.

### **Study methods**

The following demographics and clinical variables were obtained: gender, age at diagnosis and start of GLM, and location of inflammation in the gut.

Data, if available, were assessed at various time points: start of GLM, week 2 and 4, and month 3, 6, 9 and 12 after start. Data were collected, if available, at GLM start and after including C-reactive protein (CRP), serum albumin, erythrocyte sedimentation rate (ESR) at one hour and full blood count. Faecal calprotectin was used as an indirect marker for mucosal healing. Anthropometric parameters included weight, height and body mass index (BMI) for age, which were then converted to standard deviation score (Z-scores), using the WHO anthro statistical software (Version 3.2.2, 2011) [32,33].

Any concomitant therapy was ascertained and coded as dichotomous variables (absent/present) including immunomodulators and previous IFX and ADA use (including length of administration). All doses of enteral and parenteral corticoids were noted and converted to prednisone equivalents if necessary. Corticosteroid exposure was summarized as cumulative cortisone dose and as daily cortisone usage at time of visit.

### **Paediatric Crohn's Disease Activity Index**

Disease activity was assessed at each visit using paediatric Crohn's Disease Activity Index (PCDAI) [34]. PCDAI scores  $\leq 10$  were defined as remission,  $>10-30$  as mild disease and  $>30$  as moderate/severe disease activity. The outcome of PCDAI was assessed as the difference in PCDAI at the different time points. An improvement in PCDAI at the end of the study was defined as "responder" to GLM.

### **Ethics**

The institutional Ethics Committee of the University Clinics Vienna has approved this study (EK- Nr: 1697/2014) on 4<sup>th</sup> November 2014. Written, informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee. All authors had access to the study data and reviewed and approved the final manuscript.

### **Statistics**

Statistical analyses were performed with SPSS Software. Continuous variables are presented as mean, standard deviation, median, range and categorical data as absolute frequencies and proportions. The  $\chi^2$ -test, paired t-test, and t-test ANOVA were used for comparisons between frequencies, time points or disease activity groups.  $P < 0.05$  was considered to indicate statistical significance.

# Results

## Baseline patient characteristics (Table 1. and 2.)

The patient series consisted of 7 children (5 girls) with CD. The median age at diagnosis was 6.5 years (range: 2.9–15.1) and age at first GLM injection was 16.9 years (range: 9.2 to 19.1). Disease distribution at start was limited to the colon in one child. Three children had diffuse disease defined as gastroduodenal, ileal and colonic involvement. Two children had gastric and colonic involvement; one had gastroduodenal and colonic involvement. Perianal disease was present in one child.

## Previous biological treatment (Table 1.)

All patients had been consecutively treated with IFX and ADA before start of GLM. The median age at start of IFX was 12.9 years (range: 4 to 15.5). IFX had been given for a median of one year (range: 0.5 to 1.9) with a median of 11.3 (range: 7 to 12) for the number of received infusions. The median age at start of ADA was 14.6 years (range: 5.8 to 18.8). ADA has been given for a median of 1.4 years (range: 0.3 to 3.3) with a median of 11 (range: 7 to 23) for the numbers of injections. The reason of discontinuation was loss of efficacy in 6 cases and an infusion reaction in one case. Antibodies and trough levels for IFX or ADA were not routinely measured during this study period.

## GLM and dose escalation (Table 2.)

During follow up the median GLM duration was 7.2 months (range: 5.7 to 15.6 months). In 4 patients GLM doses were increased after a median of 9.7 weeks (range: 8 to 20.2 weeks) due to clinical deterioration. Dose escalation was achieved by shortening the dosing interval from four to three weeks.

## Concomitant corticosteroids and immunomodulators (Table 3.)

At start of GLM, 5 of the 7 children were on corticosteroids with a median dose of 20 mg (range: 5 to 20 mg), four of these five patients were steroid-dependent defined as weaning was not possible. The initiation of GLM made a complete steroid withdrawal possible in one case after 4 weeks and steroid reduction possible in 2 out of 4 of the steroid-dependent. This steroid tapering was possible after 3 and 6 months respectively. At the last visit four children were on steroid with a daily dose range between 5 to 55 mg.

Concomitant immune modulating therapy at GLM initiation was methotrexate in 2 cases (case 1 and 7). This was throughout the study period and was stopped after 5.9 months and 10.4 months respectively. In one other patient (case 6), treatment with cyclosporine with aimed trough levels around 150–200 ng/ml was started after three months.

## Effect of GLM on PCDAI (Fig. 1)

PCDAI scores were available for all patients at baseline with remission in one (= patient with intolerance), mild activity in one, moderate to severe activity in 5 cases. Disease activity decreased with mean PCDAI

scores falling from  $32.1 \pm 14.8$  baseline to  $25.3 \pm 17.7$  at 4 weeks ( $p = 0.13$ ), to  $28.7 \pm 19.7$  at 3 month ( $p = 0.3$ ), to  $28.9 \pm 22$  at 6 month ( $p = 0.5$ ) to  $25.3 \pm 18.6$  at last visit ( $p = 0.2$ ). At the last visit, 2 of the 7 patients had no disease activity ( $PCDAI \leq 10$ ), 3 had mild and the remaining 2 had moderate to severe disease activity. Of the 5 patients with moderate to severe disease activity at start, one showed no response to GLM (case 1), in one patient disease activity only decreased after CSA was initiated (case 6). The remaining three patients responded to GLM therapy (case 3–5). However, the first respond only shortly and developed a duodenocolonic fistula (case 5), the second had clinical response according to PCDAI but nonetheless discontinued GLM therapy due to ineffectiveness (case 4). The remaining two (case 2 and 7) adolescent with mild and no disease activity at start, disease activity remained stable during follow-up.

Weight SDS, height SDS and BMI SDS at start and during follow up were not lower compared to reference data. There was no significant improvement in weight, height and BMI SDS post GLM (for all  $p = n.s$ ).

### Effect of GLM on inflammatory markers

Serum inflammatory markers were recorded at baseline and afterwards, if available. After 2 weeks there was a significant increase in mean haematocrit from  $33.5 \pm 3.2$  to  $36.2 \pm 3.5$  ( $p = 0.04$ ), but not in the following. In week 2 to week 4 after GLM start, there was a significant increase of CRP (mean  $0.9 \pm 0.7$  to  $1.5 \pm 0.7$  mg/dl,  $p = 0.02$ ) and from week 4 to month 3 a significant increase of ESR ( $78 \pm 36.8$  to  $93 \pm 37.5$ ,  $p = 0.02$ ).

### Effect of GLM on mucosal healing

Comparing start of GLM to week 4 there was a statically significant improvement in faecal calprotectin ( $p = 0.05$ ). For all other parameters, there were no significant changes.

In 3 children histology results were available before and under treatment with GLM. The indication for endoscopy after GLM was loss of efficacy with clinical flare-up in all children. In one case active inflammation of the mucosal biopsies was persistent with no changes under GLM treatment. In two cases there was a deterioration of inflammation.

### GML and discontinuation

In two children (case 4 and 5) GLM had to be discontinued. The reason for discontinuation was loss of efficacy with persisting severe diarrhoea and abdominal pain after 7.3 months in one patient (case 4) despite improved in PCDAI. In this child GLM was used as the last treatment option before colectomy, however was switched to ustekinumab (Stelara®; Janssen Biotech, Inc., Horsham, Pa) afterwards. So further surgical procedures could be withheld due to the positive effect of GLM. The other child (case 5) developed a duodenocolonic fistula 10.2 months after GLM initiation and needed gastrointestinal surgery. Therefore, GLM was stopped preoperatively after 11.2 months. In a third child (case 1) and PCDAI non-responders GLM discontinuation might be likely in the near future, if no further clinical improvement could be seen in the next months.

## Adverse events

There were no serious adverse effects, deaths or malignancies in the study cohort during the study period. There were no opportunistic infections reported. One patient underwent a surgical procedure during the time of the study with intestinal resection for active fistulising CD.

## Discussion

This case series report on the effect of GLM in paediatric CD patients refractory and/or intolerant to previous TNF antibodies.

Our data show that GLM is effective in decreasing disease activity and maintaining clinical improvement in the majority of children with moderate to severe CD. Five of the seven patients were GLM PCDAI responders at the end of the study. The number of patients with moderate to severe disease activity could be reduced from 5 children at GLM start to two children at the end. A significant reduction in faecal calprotectin could be demonstrated after week 4. Along with clinical improvement a corticosteroid reducing effect could be achieved in 3 out of 5 children. In one child (case 4) a surgical therapy could be withheld due to the positive effect of GLM.

GLM is a transgenic fully human monoclonal immunoglobulin G1 antibody that targets a unique epitope on the TNF- $\alpha$  molecule. Preclinical work showed that the affinity of GLM for soluble and transmembrane TNF- $\alpha$ , its ability to neutralize TNF- $\alpha$  and inhibit TNF- $\alpha$ -induced cytotoxicity and human endothelial cell activation is superior to both IFX and ADA [[15](#), [35](#), [36](#)]. This report describes a cohort of patients where GLM was used as rescue therapy after all other treatment had failed to achieve remission. Our patients had been suffering from CD for years and GLM was used as a third line TNF antibody. The mean duration of IFX and ADA was around one year. The majority of our children demonstrated moderate to severe active disease by PCDAI scores before GLM therapy. Following GLM, only 2/7 patients still exhibit moderate/severe disease activity. Similar to Merras-Salmio et al, all patients responded to the first injection of GLM [28] or to Hyams et al, were at week 6 clinical response was achieved in 60% and clinical remission in 42,6% [25–27]. It can be speculated that the superior affinity of GLM to TNF- $\alpha$  and TNF- $\alpha$  induced cytotoxicity might have influenced this positive outcome.

A recent study reported the effects of GLM in 9 adults with GLM moderate to severe CD refractory to anti-TNF therapy. Patients were given either 50, 100 or 200 mg of GLM with maintenance dosing continued every 2 weeks. Six patients exhibited response by week 2 [24]. A recent published paediatric multicentre study that evaluated pharmacokinetic (PK) and clinical benefit in UC patients naïve to anti-tumor necrosis factor treatment showed that the PK efficacy, and safety outcomes observed were comparable with those previously reported in the GLM adult UC. However, serum GLM concentrations were generally lower in the < 45 kg than  $\geq$  45 kg weight subgroup. Three subjects were even positive for antibodies to GLM [25–27]. Although the majority of our patients were  $\geq$  45 kg weight subgroup, in our cohort GLM doses needed to be increased in four patients after 10 weeks. Dose escalation was achieved by reducing the dosing

interval from four to three weekly, however we did not check for GLM antibodies. This was in line with Merras-Salmio et al, where the response also did not last until the third dose at four weeks and the inflammatory markers started to increase, all their patients needed therapy escalation at two to six months [28]. However similar to Merras-Salmi et al [28], doses used in our retrospective study were heterogeneous, both cohorts included CD patients and were not naïve to anti-TNF therapy, and hence it is difficult to draw any firm conclusions about optimal dosing and compare the results with the latest PK studies in paediatric UC patients [25–27].

GLM may be intensified in cases of persistent disease activity and disease relapse, but further study including pharmacokinetics are urgently required as are the introduction of trough levels to draw further conclusion in optimal dose of GLM [[21](#), [22](#), [25](#)–[27](#)].

In adults, 5/9 (56%) patients were in a corticosteroid free remission after 12-week follow-up [[23](#)]. Sandborn et al. reported that approximately 54% of adult patients with UC treated with GLM were receiving concomitant corticosteroids at baseline. At week 54 23.2% of patients with a maintenance dose of 100 mg, and 28.2% of patients with a maintenance dose of 50 mg were in a corticosteroid free clinical remission [[22](#)]. In comparison, we had five children who received corticosteroids at initiation, four of them corticosteroid-dependent. Two of the four children were able to reduce daily steroid therapy at the end. One child receiving GLM maintenance treatment was able to discontinue corticosteroids and achieve corticosteroid free remission at week 4.

In our study, methotrexate was used as a concomitant immunomodulators in two cases and could be discontinued after good clinical response. Treatment escalation with cyclosporine was needed after three months due to loss of GLM efficacy in only one case. The use of GLM in combination with immunomodulators is still unclear. It may be that IBD patients in need of GLM should preferably receive combination treatment with an immunomodulator in order to reduce the risk of immunogenicity, although there are no sufficient data to support this yet [[21](#), [22](#)].

Given that clinical symptoms in luminal CD reflect transmural mucosal inflammation, induction of mucosal healing may provide particularly significant clinical benefits in CD [[37](#)]. Administration of TNF antibody at regular intervals has been shown to achieving and maintaining response and mucosal healing [[37](#)–39]. In this study calprotectin, an indirect marker for mucosal healing, was significantly decreased by week 4. Similar to Hymans et al, where substantial reductions in calprotectin and lactoferrin were observed from baseline to week 6 [25–27].

Mucosal biopsies were only performed in children with clinical deterioration. Since we have no histology details from the responders is it difficult to draw a conclusion about the effect of GLM on luminal disease. However in the recent study in UC children, mucosal healing as evaluated by sigmoidoscopy/colonoscopy at week 6 (Mayo endoscopy subscore  $\leq 1$ ) was achieved in 54.3% of subjects and 22.9% achieved complete healing (Mayo endoscopy subscore 0) [25–27].

In one case a duodenocolonic fistula developed under treatment. In another child however, prevention of colectomy could be achieved due to the GLM. Data for maintenance therapy and on long-term outcome of GLM are still missing, even in the adult IBD patients. So it is difficult to draw a conclusion if this treatment can reduce the need of surgical therapy.

There are limitations: this study was performed retrospectively and the sample size of is too small to draw a firm conclusion on the effect and efficacy of GLM. GLM was given only over a two-year period in our small cohort. With this short follow-up, no serious conclusions can be drawn concerning safety. However, our retrospective experience showed no major side effects such as death, malignancies or opportunistic infections comparable with Hyams et al [25–27]. Prospective long-term studies are required to define the full safety profile of the agent in treating children with IBD.

## Conclusions

In conclusion, we have demonstrated that GLM can be an effective treatment for individual paediatric CD patients unresponsive to other therapies. Our study results suggest that GLM may induce and maintain clinical improvement in children with apparent refractory CD and could even prevent one child from colectomy. The study has also highlighted the need for prospective monitoring of these patients on a national and international basis via biological registries to most accurately contextualise the risk-benefit balance of GLM in children and adolescents with IBD.

## References

1. [Parashette KR](#), [Makam RC](#), [Cuffari C](#). Infliximab therapy in pediatric Crohn's disease: a review. *Clin Exp Gastroenterol*. 2010;3:57-63.
2. Griffiths AM, Nguyen P, Smith C, et al. Growth and clinical course of children with crohn's disease. *Gut*. 1993;34(7):939–943.
3. Markowitz J, Grancher K, Kohn N, et al. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed crohn's disease. *Gastroenterology*. 2000;119(4):895–902.
4. Bell SJ, Kamm MA. Review article: The clinical role of anti-TNFalpha antibody treatment in crohn's disease. *Aliment Pharmacol Ther*. 2000;14(5):501–514.
5. Reinecker HC, Steffen M, Witthoef T, et al. Enhanced secretion of tumour necrosis factor-alpha, IL-6, and IL-1 beta by isolated lamina propria mononuclear cells from patients with ulcerative colitis and crohn's disease. *Clin Exp Immunol*. 1993;94(1):174–181.
6. Nicholls S, Stephens S, Braegger CP, et al. Cytokines in stools of children with inflammatory bowel disease or infective diarrhoea. *J Clin Pathol*. 1993;46(8):757–760.
7. Cornillie F, Shealy D, D'Haens G, et al. Infliximab induces potent anti-inflammatory and local immunomodulatory activity but no systemic immune suppression in patients with crohn's disease. *Aliment Pharmacol Ther*. 2001;15(4):463–473.

8. Borrelli O, Bascietto C, Viola F, et al. Infliximab heals intestinal inflammatory lesions and restores growth in children with crohn's disease. *Dig Liver Dis.* 2004;36(5):342–347.
9. Ruemmele FM, Lachaux A, Cezard JP, et al. Efficacy of infliximab in pediatric Crohn's disease: a randomized multi-center open-label trial comparing schedule to on demand maintenance therapy. *Inflamm Bowel Dis.* 2009;15:388–394.
10. Hyams JS, Lerer T, Griffiths A, et al. Long-term outcome of maintenance infliximab therapy in children with Crohn's disease. *Inflamm Bowel Dis.* 2009;15:816–822.
11. [Aardoom MA, Veereman G, de Ridder L.](#) A Review on the Use of Anti-TNF in Children and Adolescents with Inflammatory Bowel Disease. *Int J Mol Sci.* 2019; 23;20(10).
12. [Russell RK, Wilson ML, Loganathan S, et al. A British Society of Paediatric Gastroenterology, Hepatology and Nutrition survey of the effectiveness and safety of adalimumab in children with inflammatory bowel disease.](#) *Aliment Pharmacol Ther.* 2011;33(8):946-53.
13. [Rosh JR, Lerer T, Markowitz J, et al.](#) Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy (RESEAT) in pediatric Crohn's disease. *Am J Gastroenterol.* 2009;104(12):3042-9.
14. [Hyams JS, Griffiths A, Markowitz J, et al. Safety and Efficacy of Adalimumab for Moderate to Severe Crohn's Disease in Children.](#) *Gastroenterology.* 2012;143(2):365-74.
15. Shealy D, Cai A, Staquet K, et al. Characterization of golimumab, a human monoclonal antibody specific for human tumor necrosis factor  $\alpha$ . *MABs* 2010;2:428–439.
16. Kay J, Matteson EL, Dasgupta B, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum.* 2008;58:964–975.
17. Smolen JS, Kay J, Matteson EL, et al. Insights into the efficacy of golimumab plus methotrexate in patients with active rheumatoid arthritis who discontinued prior antitumour necrosis factor therapy: post-hoc analyses from the GO-AFTER study. *Ann Rheum Dis.* 2013
18. Smolen JS, Kay J, Doyle MK, et al. GO-AFTER study investigators Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor  $\alpha$  inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet.* 2009;374(9685):210–221.
19. Yang H, Kavanaugh A. Adverse effects of golimumab in the treatment of rheumatologic diseases. *Expert Opin Drug Saf.* 2014;13(1):103–112.
20. Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor  $\alpha$  monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum.* 2009;60:2272–2283.
21. Sandborn WJ, Feagan BG, Marano C, et al. PURSUIT-SC Study Group Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis.

- Gastroenterology. 2014;146(1):85–95.
22. Sandborn WJ, Feagan BG, Marano C, et al. PURSUIT-Maintenance Study Group Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2014;146(1):96–109.
  23. Ben-Bassat O, Iacono A, Irwin SP, Silverberg MS, Greenberg GR. Golimumab for Treatment of Moderate to Severe Anti-TNF Refractory Crohn's Disease: Open Label Experience. *Gastroenterology*, 2012;142(5):804.
  24. Hyams JS, Chan D, Adedokun OJ, Padgett L, Turner D, Griffiths A, Veereman G, Heyman MB, Rosh JR, Wahbeh G, Strauss R. Subcutaneous Golimumab in Pediatric Ulcerative Colitis: Pharmacokinetics and Clinical Benefit. *Inflamm Bowel Dis*. 2017;23(12):2227-2237.
  25. Hyams JS, Griffiths A, Veereman G, Turner D, Chan D, et al. P-097 A Multicentre Open-Label Study Assessing Pharmacokinetics, Efficacy and Safety of Subcutaneous Golimumab in Pediatric Subjects with Moderately- Severely Active Ulcerative Colitis. *Inflamm Bowel Dis*, Vol 22, suppl1, 2016, S39–S40.
  26. Xu Y, Adedokun OJ, Chan D, Hu C, Xu Z, Strauss RS, Hyams JS, Turner D, Zhou H. [Population Pharmacokinetics and Exposure-Response Modeling Analyses of Golimumab in Children With Moderately to Severely Active Ulcerative Colitis](#). *J Clin Pharmacol*. 2018 11. [Epub ahead of print]
  27. [Merras-Salmio L](#), [Kolho KL](#). Golimumab Therapy in Six Patients with Severe Pediatric Onset Crohn's Disease. *J Pediatr Gastroenterol Nutr*. 2017;64(2):272-278.
  28. IBD Working Group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. [Inflammatory bowel disease in children and adolescents: recommendations for diagnosis—the Porto criteria](#). *J Pediatr Gastroenterol Nutr*. 2005;41(1):1-7.
  29. Lennard-Jones JE. [Classification of inflammatory bowel disease](#). *Scand J Gastroenterol Suppl*. 1989;170:2-6; discussion 16-9.
  30. Levine A, Griffiths A, Markowitz J, et al. [Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification](#). *Inflamm Bowel Dis*. 2011;17(6):1314-21.
  31. WHO Child growth standards: WHO growth software: <http://www.who.int/childgrowth/software/en/>, version 3.2.2., January 2011
  32. [www.who.int/childgrowth/en/](http://www.who.int/childgrowth/en/)
  33. Hyams J, Markowitz J, Otley A, et al. Pediatric Inflammatory Bowel Disease Collaborative Research Group. [Evaluation of the pediatric crohn disease activity index: a prospective multicenter experience](#). *J Pediatr Gastroenterol Nutr*. 2005;41(4):416-21.
  34. Hutas G. Golimumab, a fully human monoclonal antibody against TNFalpha. *Curr Opin Mol Ther*. 2008;10:393–406.
  35. Lonberg N. Human antibodies from transgenic animals. *Nat Biotechnol*. 2005;23:1117–1125.
  36. [Yang LS](#)1, [Alex G](#), [Catto-Smith AG](#). The use of biologic agents in pediatric inflammatory bowel disease. *Curr Opin Pediatr*. 2012;24(5):609-14.

37. Rutgeerts P, Diamond RH, Bala M, et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc* 2006;63:433–442.
38. [Nobile S](#), [Gionchetti P](#), [Rizzello F](#), [Calabrese C](#), [Campieri M](#). Mucosal healing in pediatric Crohn's disease after anti-TNF therapy: a long-term experience at a single center. *Eur J Gastroenterol Hepatol*. 2014;26(4):458-65.

## Declarations

**Ethics Approval and Consent to participate** The institutional Ethics Committee of the University Clinics Vienna has approved this study (EK- Nr: 1697/2014) on 4<sup>th</sup> November 2014. Written, informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee. All participants or their parental guardians signed to agree to use data for prospective analysis, without any individual person's data in any form (including individual details, images or videos).

**Consent for publication** All authors had access to the study data and reviewed and approved the final manuscript. All participants or their parental guardians signed to agree to use data for prospective analysis.

**Competing interests** There is no financial or personal relationship with other people or organisations that could inappropriately influence this work. There were no financial or personal relationships with any company or organization sponsoring the research at the time the research was done.

**Funding** There is no funding. There were no financial or personal relationships with any company or organization sponsoring the research at the time the research was done.

**Author Contributions** The study was designed by JP. The subjects were recruited by JP, NM, WH and BBF. Data collection and analyses were done by JP and CA. The manuscript was written by JP with the provision of significant advice and consultation by CA. All authors critically appraised the manuscript.

**Acknowledgements** There are no acknowledgements. Not applicable

## Abbreviations

ADA- adalimumab, CD- Crohn's disease, GLM golimumab, IBD- inflammatory bowel disease, IFX- infliximab, PCDAI- paediatric Crohn's Disease Activity Index, PK- pharmacokinetics, UC- ulcerative colitis, TNF- tumor necrosis factor

## Tables

[Please see supplementary files for table 1.]

**Table 2.**

Baseline characteristics per patients receiving Golimumab (GLM)

ID	Sex	Age at diagnosis in years	Age at GLM start in years	Induction of GLM in milligram	Maintenance of GLM in milligram	GLM dosing intervall	GLM stopped at months
1	F	2,89	9,2	50/50	50	3 we after 3 mo	
2	F	5,94	16,64	200/100	50	3 we after 3 mo	
3	F	15,11	19,13	100/100	100	3 we after 3 mo	
4	M	6,51	17,83	200/100	50	4 we	7.3
5	M	12,17	18,86	50/100	100	3 we after 3 mo	11.2
6	F	12,31	16,97	200/100	50	4 we	
7	F	5,66	14,21	200/100	50	4 we	

**Table 3.**

Concomitant medications with Golimumab (GLM)

ID	Steroids in milligram start	Steroids during GLM	Steroids in milligram end	IM start	IM end
1	20	Reduction	15	MTX 15mg	MTX stopped
2	5	Withdrawal	-		
3	-	Short course	-		
4	25	Reduction	5		
5	25	Temporary weaning, increase	50		
6	5	Increase	10		CSA started
7	-	Never on steroids	-	MTX 20mg	MTX stopped

IM- immunomodulators, MTX – methotrexat, CSA- cyclosporin

## Figures

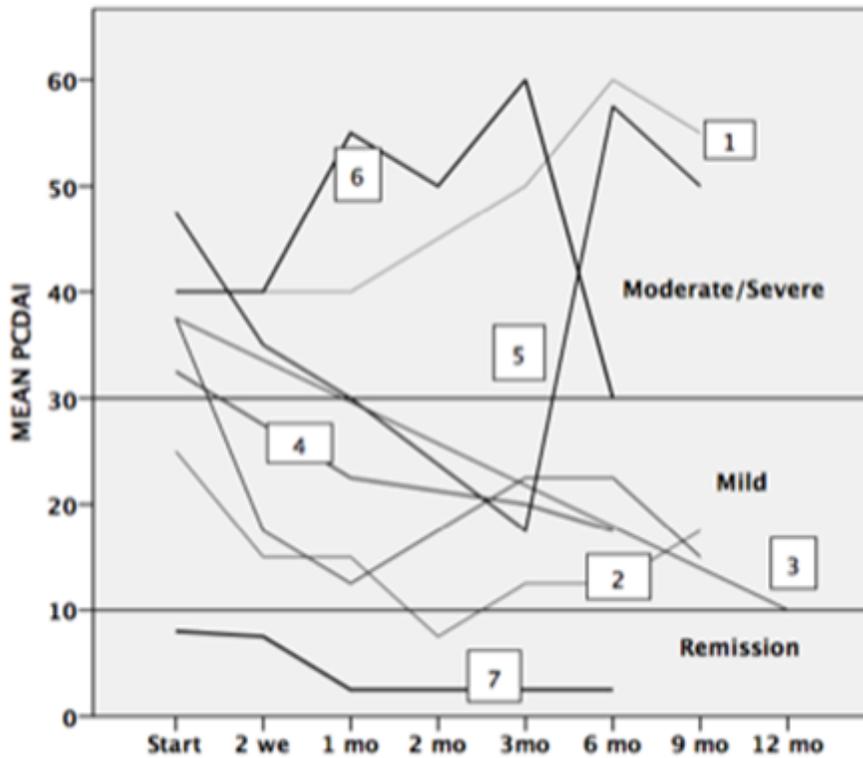


Figure 1

Effect of GLM on PCDAI

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table107.01.2019.doc](#)