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REGULAR ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

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

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Abstract

Aim: Anti-tumour necrosis factor (TNF)-α drugs are effective treatments for the management of moderate/severe Crohn's disease (CD), but treatment failure is common. 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). 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: In moderate/severe CD, golimumab induced clinical remission with PCDAI response. Golimumab may be an effective rescue therapy in refractory CD.

KEYWORDS

adolescents, clinical response, Crohn's disease, golimumab

1 | 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 tumour necrosis factor (TNF)-α, since dysregulation of TNF-α plays an important role in CD.[1,4] The number of TNF-α

Abbreviations: ADA, adalimumab; CD, Crohn's disease; GLM, golimumab; IBD, inflammatory bowel disease; IFX, infliximab; PCDAI, Paediatric Crohn's Disease Activity Index; TNF, tumour necrosis factor; UC, ulcerative colitis.

producing cells is greatly increased in the intestinal mucosa and lumen of patients with CD, and increased concentrations of TNF-α have been found in the stool of children with CD.[1,4-6]

The monoclonal chimeric anti-TNF-α antibody Infliximab (IFX, Remicade®, Merck Sharp & Dohme Corp)[7-9] and the fully human anti-TNF-α antibody, Adalimumab (ADA, Humira®, Abbott Laboratories)[9-11] 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-α antibody Golimumab (GLM, Simponi®, Janssen Biotech, Inc).[9,12] GLM has been shown to be efficacious in the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis in adults[13-16] and furthermore was approved in 2013 for the treatment of adult patients with moderate and severe active ulcerative colitis (UC).[17,18] 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-α treatment.[19]

Golimumab 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-α antibody showed at week 6 54% mucosal healing with no clinically important safety concerns.[9,20,21]

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. 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.[22]

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.

Key notes

- Golimumab induced and maintained clinical response in adolescents with Crohn's disease that did not respond to infliximab and adalimumab.
- Improvement of disease activity, reduction of steroids and discontinuation of concomitant immunomodulators could be achieved.
- Even used as a third-line TNF antibody, golimumab may reduce the need for surgery.

2 | METHODS

2.1 | 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 [23,24] and classified using Paris classification for CD.[25]

2.2 | 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 four patients were administered 200 mg, then 100 mg 2 weeks later for induction and 50 mg as maintenance. Two received induction dose and maintenance dose of 100 mg, and one child received induction dose and maintenance doses of 50 mg.

2.3 | 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 1 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).[26,27]

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 summarised as cumulative cortisone dose and as daily cortisone usage at time of visit.

2.4 | Paediatric Crohn's disease activity index

Disease activity was assessed at each visit using Paediatric Crohn's Disease Activity Index (PCDAI).[28] PCDAI scores ≤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.

2.5 | Ethics

The institutional Ethics Committee of the University Clinics Vienna has approved this study (EK- Nr: 1697/2014) on November 4, 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.

2.6 | 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-squared test, paired *t* test, and *t* test ANOVA were used for comparisons between frequencies, time points or disease activity groups. $P < .05$ was considered to indicate statistical significance.

3 | RESULTS

3.1 | Baseline patient characteristics (Table 1 and 2)

Tables 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: 9.2-19.1). 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.

TABLE 1 Baseline characteristics

Characteristics	
Number of patients[a]	7 (100%)
Female	5 (71%)
Age at diagnosis in years[b]	6.5 (2.9-15.1)
Age at first GLM injection in years	16.9 (9.2-19.1)
Disease location according to Paris classification[a]	
L1 Small intestine	-
L2 Colon	2 (29%)
L3 Small intestine and colon	4 (57%)
L4a Upper gastrointestinal tract	5 (71%)
Perianal disease	1 (14%)
Granuloma	1 (14%)
IBD-related medications at start of golimumab	
Corticosteroids	5 (71%)
5-Aminosalicylic acid	6 (85%)
Methotrexate	2 (29%)
Biologics	
Prior IFX use	7 (100%)
Duration of prior IFX use in years[b]	1 (0.5-1.9)
Number of IFX infusion[b]	11.3 (7-12)
IFX trough levels	31.6 (0.5-54)
Allergic reactions to IFX[a]	1 (14%)
Prior ADA use	7 (100%)
Number of children on ADA at start of golimumab,	6 (85%)
Duration of prior ADA use in years[b]	1.4 (0.3-3.3)
Number of ADA injection[b]	11 (7-23)

Abbreviations: ADA Adalimumab; IXF infliximab.
[a]Results are presented as number (% of total).
[b]Results are presented as median (range).

3.2 | Previous biological treatment (Table 1)

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: 4-15.5). IFX had been given for a median of 1 year (range: 0.5-1.9) with a median of 11.3 (range: 7-12) for the number of received infusions. The median age at start of ADA was 14.6 years (range: 5.8-18.8). ADA has been given for a median of 1.4 years (range: 0.3-3.3) with a median of 11 (range: 7-23) 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 ADA were not routinely measured during this study period.

3.3 | GLM and dose escalation (Table 2)

Table 2 during follow-up, the median GLM duration was 7.2 months (range: 5.7-15.6 months). In four patients, GLM doses were increased after a median of 9.7 weeks (range: 8-20.2 weeks) due to clinical deterioration. Dose escalation was achieved by shortening the dosing interval from 4-3 weeks.

3.4 | Concomitant corticosteroids and immunomodulators (Table 3)

Table 3 at start of GLM, five of the seven children were on corticosteroids with a median dose of 20 mg (range: 5-20 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 and 55 mg.

Concomitant immune modulating therapy at GLM initiation was methotrexate in 2 cases (case 1 and 7). This was throughout the

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 interval	GLM stopped at months
1	F	2.89	9.2	50/50	50	3 wk after 3 mo	
2	F	5.94	16.64	200/100	50	3 wk after 3 mo	
3	F	15.11	19.13	100/100	100	3 wk after 3 mo	
4	M	6.51	17.83	200/100	50	4 wk	7.3
5	M	12.17	18.86	50/100	100	3 wk after 3 mo	11.2
6	F	12.31	16.97	200/100	50	4 wk	
7	F	5.66	14.21	200/100	50	4 wk	

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 15 mg	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 20 mg	MTX stopped

Abbreviations: CSA, cyclosporin; IM, immunomodulators; MTX, methotrexat.

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 through levels around 150-200 ng/mL was started after 3 months.

3.5 | Effect of GLM on PCDAI (Figure 1)

Figure 1 PCDAI scores were available for all patients at baseline with remission in one (= patient with intolerance), mild activity in one and moderate-to-severe activity in 5 cases. Disease activity decreased with mean PCDAI scores falling from 32.1 ± 14.8 baseline to 25.3 ± 17.7 at 4 weeks ($P = .13$), to 28.7 ± 19.7 at 3 months ($P = .3$), to 28.9 ± 22 at 6 months ($P = .5$) and to 25.3 ± 18.6 at last visit ($P = .2$). At the last visit, 2 of the 7 patients had no disease activity (PCDAI ≤10), three had mild, and the remaining two had moderate-to-severe disease activity. Of the five patients with moderate-to-severe disease activity at start, one showed no response to GLM (case 1), and 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), and 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).

3.6 | 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 ± 3.2 to 36.2 ± 3.5 ($P = .04$), but not in the following. In week 2 to week 4 after GLM start, there was a significant increase of CRP (mean 0.9 ± 0.7-1.5 ± 0.7 mg/dL, $P = .02$) and from week 4-month 3 a significant increase of ESR (78 ± 36.8-93 ± 37.5, $P = .02$).

3.7 | Effect of GLM on mucosal healing

Comparing start of GLM to week 4, there was a statically significant improvement in faecal calprotectin (1651 ± 75-262 ± 36, $P = .05$). 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,

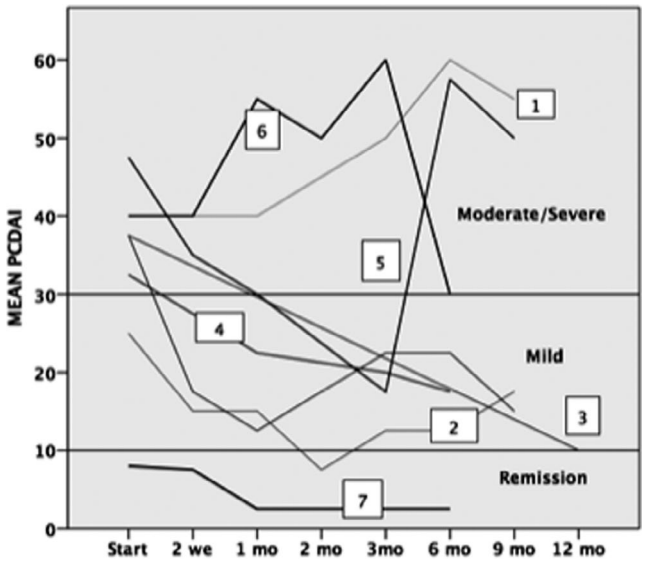

FIGURE 1 Effect of GLM on PCDAI

active inflammation of the mucosal biopsies was persistent with no changes under GLM treatment. In two cases, there was a deterioration of inflammation.

3.8 | GML and discontinuation

In two children (cases 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) 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.

3.9 | 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.

4 | DISCUSSION

This case series reports on the effect of GLM in paediatric CD patients refractory and/or intolerant to previous TNF antibodies. The data suggest that GLM might have the capacity to decrease disease activity in a proportion of children with CD although they formerly have been shown to be refractory to other anti-TNF drugs.

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.

Golimumab is a transgenic fully human monoclonal immunoglobulin G1 antibody that targets a unique epitope on the TNF-α molecule. Preclinical work showed that the affinity of GLM for soluble and transmembrane TNF-α, its ability to neutralise TNF-α and inhibit TNF-α-induced cytotoxicity and human endothelial cell activation is superior to both IFX and ADA.[12,29,30] 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 1 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,[22] or to Hyams et al, were at week 6 clinical response was achieved in 60% and clinical remission in 42.6%.[20,21] It can be speculated that the superior affinity of GLM to TNF-α and TNF-α-induced cytotoxicity might have influenced this positive outcome.

A recent study reported the effects of GLM in 9 adults with GLM moderate/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.[19] A recent published paediatric multicentre study that evaluated pharmacokinetic and clinical benefit in UC patients naïve to anti-tumour necrosis factor treatment showed that pharmacokinetic 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 ≥45 kg weight subgroup. Three subjects were even positive for antibodies to GLM.[20,21] Although the majority of our patients were ≥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 4 weeks and the inflammatory markers started to increase, all their patients needed therapy escalation at two to 6 months.[26] GLM may be intensified in cases of persistent disease activity and disease relapse, but further studies including pharmacokinetics are urgently required as are the introduction of trough levels to draw further conclusion in optimal dose of GLM.[16,17,19,20]

In adults, 23%-56% of patients were in a corticosteroid free remission after 12-week follow-up.[17,18] 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 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 is too small to draw a firm conclusion on the effect and efficacy of GLM. Only IFX trough levels were available. No ADA levels were taken, so it is difficult to exclude whether our patients were really refractory to ADA. However, dose intervals were shortened to weekly and doses doubled for in total 3 times in case of flare-up. Some of the patients were on combined immunomodulators before GLM was started, which were common practices before ADA trough levels were available. GLM was given only over a 2-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[20,21] Prospective long-term studies are required to define the full safety profile of the agent in treating children with IBD.

5 | CONCLUSIONS

In conclusion, we have demonstrated that GLM can be an effective treatment for paediatric CD patients unresponsive to previous TNF therapies. In one child, colectomy could be prevented. Although our data seem promising, further studies with a higher number are required to evaluate whether GLM plays an additional role, since biologicals with various pathways are already available or wait in pipeline. 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.

CONFLICT OF INTEREST

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 organisation sponsoring the research at the time the research was done.

ETHICAL APPROVAL

The Institutional Ethics Committee of the University Clinics Vienna has approved this study (EK- Nr: 1697/2014) on November 4, 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.

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