TNF-alpha antagonists and thalidomide for the management of gastrointestinal Behçet's syndrome refractory to the conventional treatment modalities: a case series and review of the literature

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ABSTRACT

Objective. *Gastrointestinal involvement of Behçet's syndrome is usually treated with glucocorticoids, 5-aminosalicylic acid compounds and azathioprine. However, some patients are refractory to these conventional therapy modalities. In this paper we report our experience on 13 patients with gastrointestinal involvement of Behçet's syndrome who were refractory to the conventional therapy and who were treated with TNF-alpha antagonists and/or thalidomide.*

Methods. *We reviewed the charts of our Behçet's syndrome patients with gastrointestinal involvement and identified those who were treated with TNF-alpha antagonists and/or thalidomide. Demographic features, previous and concomitant drugs, previous surgery, time to remission and duration of remission were tabulated. We also performed a systematic review of publications on gastrointestinal involvement of Behçet's syndrome patients treated with TNF-alpha antagonists and/or thalidomide.*

Results. *Among our 64 patients with gastrointestinal involvement of Behçet's syndrome, we identified 13 (20%) (7 women, 6 men, mean age 27.4 ± 9.4) who had been treated with TNF-alpha antagonists and/or thalidomide. Their previous medications were glucocorticoids (13/13), azathioprine (13/13), 5-aminosalicylic acid derivatives (3/13) and budesonide (1/13). Clinical and endoscopic remission was obtained in 10 patients. One patient died with sepsis. The systematic literature search revealed 91 cases who had used TNF-alpha antagonists and 15 who had used thalidomide. Among the patients who had received TNF-alpha antagonists, clinical remission was obtained in 47/91 patients (51%), while endoscopic remission was observed in 21/46 (45%) who had a control colonoscopy.*

Conclusion. *One fifth of our Behçet's syndrome patients with gastrointestinal involvement were refractory to conventional treatment modalities. Remission was obtained with TNF-alpha antagonists and/or thalidomide in about 75 % of the cases.*

Introduction

Gastrointestinal involvement of Behçet's syndrome (GIBS) is characterised by gastrointestinal ulcers that are located mainly in the ileocecal region. These ulcers can also be located in the other colonic segments, small intestine, oesophagus or duodenum. GIBS may cause abdominal pain, diarrhoea, fever or weight loss. The main complications are perforation, bleeding and fistula formation (1). Surgical interventions can be necessary in some patients due to acute complications such as acute abdomen or bleeding and in others due to persistent symptoms despite medical therapy (2). The prevalence of GIBS shows differences depending on the geographic distribution. It is more frequent in the Far East including Japan and Korea and the United States, compared to the Middle East and Europe (3). This difference may be related to several factors such as genetic and environmental factors, as well as the diagnostic methods and criteria used (1). The management of GIBS is similar to inflammatory bowel diseases in terms of the medications used. The conventional treatment modalities are glucocorticoids, azathioprine, salazopyrine and other 5-aminosalicylic acid (5-ASA) derivatives (4). Some patients with GIBS can be refractory to these agents, necessitating other medical options. TNF-alpha antagonists and thalidomide are the main options in such cases. TNF-alpha antagonists have been used with increasing frequency

in ocular, neurological, mucocutaneous and vascular complications of Behçet's syndrome (BS) (5). There are relatively few reports on the use of these agents for gastrointestinal involvement.

In this paper we report our experience with 13 refractory GIBS patients who were treated with TNF-alpha antagonists and/or thalidomide. We also performed a systematic review of publications reporting on treatment of GIBS patients with TNF-alpha antagonists and/or thalidomide.

Materials and methods

We reviewed the charts of all of our patients with GIBS and identified those who were treated with TNF-alpha antagonists and/or thalidomide for gastrointestinal involvement. We determined the demographic features, initial clinical manifestations, endoscopic and histologic findings of these patients from patient charts using a standard form. Data regarding management including previous and concomitant drugs, previous surgery, the dose and duration of TNF-alpha antagonists and thalidomide, time to remission and duration of remission were recorded. Data on outcome were obtained from patient charts for patients who had visited the clinic for their routine controls during the last 3 months. Patients who had not visited the clinic during the last 3 months were called to the clinic for a final evaluation.

In our department the usual management strategy of GIBS is with immunosuppressive therapy, mainly azathioprine (2–2.5 mg/kg). Additional glucocorticoids are used in patients with obstructive symptoms and/or uncontrollable diarrhoea. Maximum dose is usually equivalent to 32 mg of methylprednisolone which is tapered and stopped within 2 to 3 months. Azathioprine is continued for at least 1 year after endoscopic remission is obtained. 5-ASA derivatives may be tried instead of azathioprine in mild cases with only superficial ulcers. Patients who are refractory to these agents were treated with thalidomide before TNF-alpha antagonists were available. Such patients are now treated mainly with TNF-alpha antagonists.

In this paper we used the term "refractory" if the conventional treatment modalities did not result in remission. "Clinical remission" was defined as disappearance of all gastrointestinal system related symptoms and "Endoscopic remission" was defined as complete disappearance of gastrointestinal ulcers.

Systematic literature search

We performed a systematic literature search in PubMed using the keyword combination: "Behçet AND (infliximab OR adalimumab OR etanercept OR golimumab OR certolizumab OR thalidomide)" for articles published until December 2014. We searched for meta-analyses, systematic reviews, randomised controlled trials, controlled clinical trials, clinical trials, observational studies, and case reports of BS patients treated with TNF-alpha antagonists and/or thalidomide for gastrointestinal involvement. We considered no language or age limitation. We also performed a hand search of the references of the retrieved studies. We excluded manuscripts which included BS patients who were treated with TNF-alpha antagonists or thalidomide for other types of BS involvement.

We retrieved the demographic features, location of gastrointestinal involvement, previous and concomitant medications, previous surgery, type, dose and duration of the TNF-alpha antagonist or thalidomide, outcome, time to remission, and duration of remission from these manuscripts. We tried to contact the authors if these data could not be retrieved clearly from the published manuscript.

Results

There are more than 9000 recorded BS patients in our multidisciplinary BS outpatient clinic. Among these 64 have been diagnosed with GIBS and are being jointly followed in our inflammatory bowel disease outpatient clinic, together with Crohn's disease and ulcerative colitis patients. Among these 64, we identified 13 (20%) patients who were treated with infliximab, adalimumab, etanercept and thalidomide for gastrointestinal involvement (Table I). The main reason for the use of these agents was refractory disease despite conventional medical treatment and in 5 of the patients additional surgical treatment.

Seven of these patients were women and 6 were men. The mean age was 37.1±10.2 and the mean age at diagnosis of GIBS was 27.4±9.4 years. The location of involvement was ileocecal region in 7 patients, colon in 4 patients, ileum in 1 patient and duodenum in 1 patient. Among these patients 5 had undergone surgery for perforation and 1 for abdominal pain due to refractory duodenal ulcer. The previous medications that were used in these patients were glucocorticoids (13/13), azathioprine (13/13), 5-ASA (3/13, 23%) and budesonide (1/13, 7.6%) (Table II).

Among these 13 patients, one who had used infliximab died due to sepsis following a severe pneumonia. Clinical and endoscopic remission was obtained in 10 patients. One patient remained unresponsive despite thalidomide and had remission only after surgery. One other patient could not be controlled with thalidomide, infliximab and adalimumab, but remission was achieved after stem cell transplantation for concomitant myelodysplastic syndrome associated with trisomy 8.

Thalidomide

Among the 13 patients, 6 were prescribed thalidomide (5 patients 100 mg/day, 1 patient 50 mg/day). Remission was obtained in four of these six patients. One of these patients had had right hemicolectomy for ileocecal perforation and azathioprine was started. One year later, although she did not have any clinical symptoms, an ulcer was observed at the anastomosis site during her control endoscopy and thalidomide was started in addition to azathioprine. The ulcer had disappeared and colonoscopy was normal 2 months after starting thalidomide. Thalidomide was stopped after 1 year and azathioprine after 5 years. The patient was lost to follow-up after this. The second patient who achieved remission with thalidomide was operated for transverse colon perforation and azathioprine was started following the operation. He had a second operation one year later due to a stenosis at the anastomosis site. Aza-

Table I. Demographic features and other BS manifestations of refractory GIBS patients.

Age /sex	Symptoms	Gastrointestinal lesion	Other BS manifestations
33/F	Abdominal pain, weight loss, fever	Pancolitis	OU, GU
20/F	Abdominal pain	Ulcer at ileocecal valve	OU, GU
25/F	Abdominal pain	Perforation at ileocecal valve, postop recurrence at descending colon and neoterminal ileum	OU, GU, OF, EN, uveitis
14/F	Abdominal pain	Perforation at terminal ileum, ileum resection, postop recurrence	OU, GU, OF, EN, arthritis
37/F	Abdominal pain	Ulcer at cecum	OU, GU, arthritis, sacroiliitis
45 /M	Abdominal pain, fever	Ileocecal perforation, right hemicolectomy, postop recurrence and enterocutaneous fistula	OU, GU, OF, EN, Thrombophlebitis, uveitis
35/M	Bloody diarrhea	Left colon involvement, perianal fistula	OU, GU
39/F	Abdominal pain	Ulcer at ileocecal valve	OU, GU, uveitis
20/M	Abdominal pain	Ulcer at ileocecal valve	OU, GU, EN, uveitis
22/M	Abdominal pain, weight loss	Ileocecal involvement	OU, GU, OF
19/F	Abdominal pain, vomiting	Ileocecal perforation Postop recurrence with ileal ulceration obstructive symptoms, postop recurrence	OU, GU, OF, EN

BS: Behçet's syndrome; GIBS: Gastrointestinal involvement of Behçet's syndrome; F: female; M: male; OU: oral ulcer; GU: Genital ulcer; OF: Osteofolliculitis; EN: Erythema nodosum.

thioprine was continued. Six months later an ulcer was detected at the anastomosis site and thalidomide was added. His colonoscopy was normal 2 months after starting thalidomide. He used thalidomide for 14 months and azathioprine for 10 more years. He did not experience any further relapses and is being followed without treatment for the last 2 years. The third patient who responded well to thalidomide had used azathioprine for 1 year before thalidomide, and thalidomide was added due to a large ileocecal valve ulcer. Clinical remission was observed in 4 weeks and endoscopy was normal at 6 months. He used thalidomide together with azathioprine for 3.5 years and azathioprine only for 2 more years without any relapses. The fourth patient had severe eye involvement and infliximab was started when gastrointestinal involvement was diagnosed. One month later her abdominal pain was continuing and colonoscopy showed that the ulcer in her terminal ileum had persisted. Thalidomide was added. Her colonoscopy was normal at 6 months and clinical symptoms had disappeared. She is currently doing well with thalidomide and infliximab, 14 months after the initiation of thalidomide. Among the 2 patients who did not respond well to thalidomide, infliximab was started in one, after 5 years of thalidomide use with occasional relapses controlled with high dose corticosteroids. Surgery was necessary in the other patient for a duodenal ulcer that persisted for 6 months despite thalidomide and azathioprine treatment. He achieved remission after surgical resection and is doing well without any medications for the last 8 years. The only adverse event these patients experienced was mild day-time sleepiness that was observed in 5 of the 6 patients.

Infliximab

A total of 8 patients were prescribed infliximab, including the patient mentioned above, who continued to have relapses with thalidomide. TNF-alpha antagonists have generally replaced thalidomide for the management of gastrointestinal involvement, after they became available in Turkey. The usual dose of infliximab was 5 mg/kg given at baseline, 2nd and 6th weeks and every 8 weeks thereafter, except in one patient whose dose was later increased to 10 mg/kg. These patients had previously used azathioprine for a mean duration of 8.2±6.4 months before infliximab. Infliximab was started postoperatively after ileocecal or ileal perforations in 3 of the patients. The reason for starting infliximab was resistant clinical findings including abdominal pain and bloody diarrhea in the remaining 5 patients. Endoscopy had shown ileocecal ulcers in 3, pancolitis in 1 and left sided colitis in 1 patient. Concomitant medications were corticosteroids in 2 patients, azathioprine in 6 patients and cyclophosphamide (for pulmonary artery thrombosis) in 1 patient.

Among the 8 patients who were prescribed infliximab, one died due to pneumonia followed by respiratory failure and sepsis as previously mentioned. This patient had received 3 infliximab infusions and still had active gastrointestinal involvement. He additionally developed pulmonary artery thrombosis and cyclophosphamide and high dose pulse glucocorticoids were given. He developed pneumonia shortly after this which progressed to sepsis and the patient died. Remission was obtained in five of the 8 patients who used infliximab. Time to clinical remission was 2±1.2 weeks (1–4 weeks). Their control colonoscopies which were performed 11.6±7.2 weeks (6-24) after starting infliximab, also showed remission. Currently, only the patient who is using infliximab together with thalidomide is still continuing treatment. The other 4 who achieved remission, have stopped infliximab after 23.5±13.8 months of treatment and are doing well without medical therapy for 22.7±25.9 months. Apart from the patient who died, 2 patients did not have a sufficient response to infliximab despite treatment for 9 and 16 months. Adalimumab was prescribed to these two patients.

Table II. Treatment and outcome of refractory GIBS patients.

Previous tx	Tx for refractory disease	Concomitant Tx	Outcome / remission
AZA GC	IFX →ADA	None	Remission achived with stem cell transplantation
SSZ AZA GC Budesonide	IFX→ADA	GC AZA Budesonide	CR ER
GC AZA Cyc-A Ileocecal resection	Thalidomide → IFX	AZA	CR ER
5-ASA GC AZA	IFX	AZA	CR ER
AZA	IFX	AZA	ER
AZA Cyc-A INF GC Right hemicolectomy	IFX	Pulse GC Cyc-A	There is no endoscopic either clinical response. Died due to infectious complications.
5ASA AZA	IFX	AZA	CR ER
GC AZA Cyc-A INF ANAKİNRA CANAKİNUMAB	IFX → ADA→ IFX + THD	AZA THD	CR ER
AZA Cy A	ETA	None	CR ER
GC AZA	THD	AZA	CR ER
Right hemicolectomy AZA	THD	AZA	ER
PPI AZA AZA	THD THD	- AZA	Unresponsive to medical therapy. Surgical therapy performed Remission at endoscopy

5-ASA: 5-aminosalicylic acid 6-MP: 6-Mercaptopurine ADA: Adalimumab; AZA: Azathioprine; Co: Colchicine; CR: Clinical Remission Cyc-A: cyclosporine A; Cyc: Cyclophosphamide; ETA: Etanercept; ER: Endoscopic remission; GC: Corticosteroids; GIBS: Gastrointestinal involvement of Behçet's syndrome; IFX: Infliximab; INF: Interferon; SSZ: Sulphasalazine; THD: Thalidomide; Tx: Therapy.

Adalimumab

Adalimumab was given according to the Crohn's disease protocol, starting with 160 mg, decreasing to 80 mg in the second injection and to 40 mg in the third injection and thereafter (6). One of the patients who was prescribed adalimumab achieved clinical remission in 2 weeks. It was observed that she also achieved endoscopic remission, when a control endoscopy was performed at 3 months. She received adalimumab for 12 months without any relapses and is currently being followed for the last 12 months without any medications. The other patient continued to have active gastrointestinal involvement despite adalimumab for 15 months. At this time she developed myelodysplastic syndrome associated with trisomy 8. Stem cell transplantation had to be performed for the myelodysplastic syndrome and she achieved clinical and endoscopic remission after this. She is still doing well 8 months after stem cell transplantation (7).

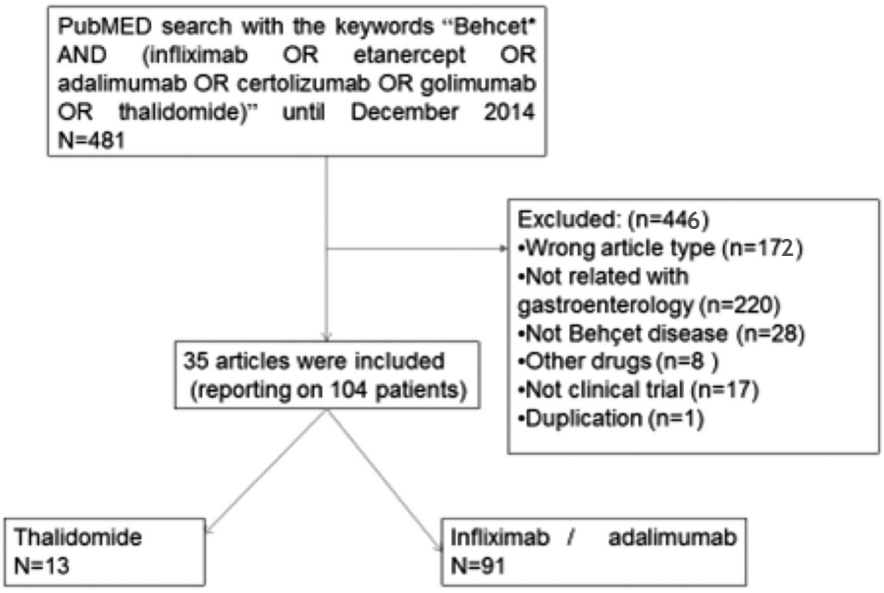

Fig. 1. Flow chart of the Pubmed search.

Etanercept

One patient with uveitis and ileocecal ulceration who was unresponsive to cyclosporine A and azathioprine, was prescribed etanercept 25 mg twice per week for controlling both eye and gastrointestinal involvement. He had clinical gastrointestinal and endoscopic remission within 1 month. However his uveitis attack was continuing and interferon-alpha was started instead of etanercept. He has been followed for 11 years without further gastrointestinal relapses. Interferon-alpha was also stopped 3 years ago when long-term remission of uveitis was obtained.

Systematic literature review

The literature review revealed 35 articles reporting cases or case series of BS patients with gastrointestinal involvement who had been treated with TNF-alpha antagonists and/or thalidomide (Fig. 1) (8-42). A total of 13 patients who were prescribed thalidomide (Table III) and 91 patients who were prescribed TNF-alpha antagonists (Table IV) were reported in these articles.

Thalidomide

There were 13 cases who were treated with thalidomide for GIBS (8 men, 5 women, mean age 24±17.2 years) (Table III). Glucocorticoids (9/13, 69.2 %), azathioprine (5/13, 38.4%), and cy-

Table III. Thalidomide use reported in previous studies.

Reference	N/sex/ Age	GI location	Previous treatment	Tx for refractory GIBS (dose/duration)	Concomittant therapy	Outcome time to remission	Duration of maintained remission	Side effects
8	7(3F4M) / 17.5±8.7	I+C (n=2) NA (n=5)	GC (n=2) GC+AZA+Cyc-A (n=1) AZA+Cyc-A (n=1) AZA+ MTX+Cyc-A (n=1) AZA (n=1) None (n=1)	THD 25-150 mg	None	Clinical remission in all of the patients	17.5±8.7 m	None
9	1M/24	CE + I ileum perforation (2 times)	GC AZA Cyc	THD 100 mg (after second perforation)	Cyc GC	Clinical remission	4 m	NA
10	F/1	NA	GC	THD 125 mg	GC	Clinical remission	NA	NA
11	M/40	I+C	GC	THD 400 mg	GC	Clinical remission	NA	NA
12	M/35	C	GC	THD100-300mg	GC	Clinical remission endoscopic response	5 m	None
13	M/24	Transverse colon perforation post-op recurrence	GC	THD 50 mg	GC	Clinical remission and endoscopic remission	8m	Somnolence and jerks at extremities
14	M/55	Colon	GC	THD 300 mg	GC	Unresponsive colectomy required	-	NA

AZA: Azathioprine; C: Colon; CE: Cecum; Cyc-A: Cyclosporine A; Cyc: Cyclophosphamide; GC: Glucocorticoid; I+C: Ileum and colon; I: Ileum; m: Month; M: Male; MTX: Methotrexate; THD: Thalidomide; Tx: Therapy.

closporine-A (2/13, 15.3%) were used in these patients before thalidomide. Concomitant glucocorticoids were used in 6/13 (46.1%) patients and cyclophosphamide in one patient.

Clinical remission was obtained in 12 of these 13 patients (92.3%). Colectomy had to be performed in the patient who was unresponsive. A control endoscopy was reported in 2 patients. One of them had endoscopic remission and the other had improvement in his endoscopic findings. The only adverse event that was reported was somnolence and extremity jerks in 1 patient.

TNF-alpha antagonists

Among the 91 cases who had used TNF-alpha antagonists for gastrointestinal involvement, 48 were men and 43 were women, the mean age was 33.6±14.5 years (range 5–63 years). All patients except for one, had used infliximab. Only 4 patients had used adalimumab, and one had used etanercept. Three of the patients who had used adalimumab and the patient who had used etanercept had been switched to these agents after infliximab.

Among the 90 patients who had used infliximab, the indication for infliximab use was failure to obtain remission despite conventional treatment, or having recurrences when steroids were tried to be reduced or stopped. Three patients had used infliximab as initial therapy without concomitant or prior conventional therapy. The first one was a patient with oesophageal perforation with fistula formation (27), the second one was a patient with severe lower gastrointestinal bleeding (26) and in both of them infliximab was effective. The third case had colonic involvement and infliximab was not effective (25). In the rest of the group, corticosteroids (74/90, 82%) and disease modifying agents (azathioprine/6-mercaptopurine: 39/90, 43%; methotrexate: 15/90, 16.6%; cyclosporine-A: 9/90, 10%; thalidomide: 3/90, 3%; and 5-ASA: 58/90, 64%) were tried before infliximab. Twelve (13%) patients had a history of surgery, and infliximab was used in the postoperative period due to recurrence.

Infliximab therapy was combined with glucocorticoids in 31/90 (34%), and disease modifying agents (azathioprine/ 6-MP in 20/90, 22%; methotrexate in 13/90, 14%; 5-ASA derivatives in 25/90, 27%; and thalidomide in 1/90, 1%). Eight patients had not used concomitant therapy (8%). Information on concomitant therapy was not provided in 30/90 cases (33%).

Clinical remission was obtained in 46/90 patients (51%). A control endoscopy was performed in 46 of the patients and remission was observed in 21 of these (45%). All of the patients who achieved endoscopic remission also had clinical remission, fulfilling the definition for complete remission for inflammatory bowel diseases. These patients were followed for a mean duration of 26.2±17 months (range 2–58 months) and were still in remission when they were reported. In 2 patients with rectovaginal fistula complete closure was obtained. These 2 patients had had fistula formation after episiotomy. Among the 90 patients who had used infliximab, 2 deaths were reported, both due to infectious complications. In addition, 1 patient with recurrent

Table IV. Anti-TNF therapy in gastrointestinal Behçet's syndrome reported in previous studies.

Ref.	N / Sex / Age	GI location	Previous tx	Tx	Concomitant therapy	Outcome/remission
Ideguchi (15)	7/ (3M 4F) / 41 [1]	I CE C E	GC AZA 6-MP Co Cyc-A MTX 5-ASA SSZ	IFX	GC AZA 6MP Co 5 -ASA	Clinical and endoscopic remission in 1
Tanaka (16)	1 /M / 59	I+CE+C	GC 5-ASA Co Cyc-A	IFX	None	Unresponsive
Shimuzu (17)	1/F/63	stomach	GC	IFX →ADA	None	Clinical and endoscopic remission
Toyonaga (18)	2/ F /32	I+CE / I+C	5-ASA Co GC	IFX	MTX GC 5-ASA	unresponsive
Li (19)	1/ M /23	D + J	GC Co 5-ASA THD Cyc	IFX	NA	Clinical response
Kinoshita (20)	15 /(7M8F) / 46.2 [1]	C I+CE I Anastamosis	surgical operation GC 5-ASA AZA Co	IFX	GC AZA 5-ASA Co	Endoscopic and clinical remission in 4
Lee (21)	28 /(15M13F) / 35 [2]	IC C	surgical operation GC 5-ASA AZA Cyc-A Co	IFX	NA	Clinical remission in 9
Maruyama (22)	1/ F /28	IC + E	GC AZA 6-MP 5-ASA	IFX	GC 6-MP AZA	Clinical and endoscopic remission
Watanabe (23)	1 /F/5	C	GC Co IFX	ETA	Tacrolimus GC Mizoribine	Clinical remission
De Cassan (24)	1/ F /21	I + C + J	GC	ADA	GC	Clinical remission
Iwama (25)	1/ F/15	I	GC AZA Cyc-A Co	IFX	GC AZA	Clinical remission
Iwata (26)	10/ (7F 3M) / 37.7[1]	I+CE	GC AZA MTX Co SSZ 5-ASA Cyc	IFX	MTX 5-ASA Co SSZ	Clinical remission in all Endoscopic remission obtained in 9/10
Kaneko (27)	1/ M/18	E+I+C	GC pulse	IFX	NA	Clinical remission
Kwok (28)	1/M/52	E+ I	GC SSZ	IFX	None	Endoscopic response
Ariyachaipunich (29)	1 /F/30	CE+ C	GC AZA IFX	IFX → ADA	AZA	Clinical remission
Naganuma (30)	6 /(3F 3M) / 39.9[1]	I ICV CE C	AZA GC MTX 5-ASA Co Cyc-A	IFX	GC AZA	Clinical remission in 4
Ugras (31)	1 /F /12	C	5-ASA GC AZA Co	IFX	GC AZA 5-ASA	Clinical remission
Lee (32)	1/ M /47	Anastomosis	GC AZA SSZ	IFX	None	Clinical remission endoscopic response
Byeon (33)	1 /F/49	I	GC Co MTX AZA	IFX	5-ASA GC Co AZA	Clinical and endoscopic remission
Chawla (34)	1/ F/33	RVF	THD dapson	IFX	None	Fistula closure
Yuksel (35)	1/ F/1.5	C+ RVF	MTX	IFX	MTX GC	Fistula closure
Ju (36)	1/M/42	I	GC Co	IFX	None	Endoscopic remission
Van Laar (37)	1/M /34	C	GC IFX	ADA	GC MTX Cyc-A 5-ASA	Incomplete Clinical remission
Yucel (38)	1/M/56	CE+ C	None	IFX	None	Stopped due to erythema nodosum
Kram (39)	1/F/35	I+ ICV +C	None	IFX	GC AZA MTX	Endoscopic remission
Mussack (40)	1/F/21	E	None	IFX	AZA	Clinical remission
Hassard (41)	1/F/45	I+ C	GC AZA 5-ASA	IFX	GC	Clinical remission Endoscopic response
Travis (42)	1/F/27 1/F/30	C PAF C	GC THD GC Co Cyc-A	IFX THD IFX	THD None	Fistula closure Clinical and endoscopic remission

[1] Mean ±SD; [2] Median 5-ASA: 5-aminosalicylic acid 6-MP: 6-Mercaptopurine ADA: Adalimumab; AZA: Azathioprine; C: Colon; CE: Cecum; Co: Colchicine; Cyc-A: Cyclosporine A; Cyc: Cyclophosphamide; D: Duodenum; E: Esophagus; ETA: Etanercept; F: Female; GC: Corticosteroids; I: Ileal; IC: Ileocecal; ICV: Ileocecal valve; IFX: Infliximab; IVIG: Intravenous immunoglobulins; J: Jejunum; M: Male; PAF: Perianal fistula; RVF: Rectovaginal fistula; SSZ: Sulphasalazine; THD: Thalidomide; Tx: Therapy.

pneumonia and sepsis, 8 patients with infusion reactions, 1 patient with fever attributed to infliximab, 1 patient with acute respiratory distress syndrome, 1 patient with lichenoid lesions and 1 patient with erythema nodosa were reported.

There were 4 case reports about adalimumab use in GIBS (Table IV). One of these cases was actually in remission with infliximab, switched to adalimumab with her own wish and continued to be in remission with adalimumab. Two other patients who were unresponsive to infliximab were treated with adalimumab. One of them obtained clinical remission and the other still had lesions on his last endoscopy. The fourth patient who was steroid dependent was treated with adalimumab and clinical remission was obtained.

Etanercept was used in a child with colonic involvement who had an infusion reaction with infliximab, and clinical remission was obtained after etanercept therapy. No adverse events were reported with adalimumab or etanercept.

Discussion

BS is a variable vessel vasculitis and its pathogenesis is still obscure. Th-1, Th-17, natural killer cells and neutrophils take role in the inflammatory processes of BS. These cells produce cytokines such as TNF alpha IL-6 IL-17 IL-1B (43, 44). It has been reported that serum level of TNF alpha in response to LPS stimulation was increased in active BS patients compared to controls (45). Accumulation and activation of Gamma delta T cells in active inflammation sites in BS patients were reported (46). These lymphocytes express increased levels of TNF-alpha receptors (47). It was reported that infliximab suppressed gamma delta T cells expression and cytokine activity in BS (48). Taken together these may explain how anti-TNF therapy may suppress inflammation in BS (49). Thalidomide is effective in mucocutaneous lesions of Behçet's syndrome and also in anti-TNF resistant Crohn's disease and ulcerative colitis cases (50-52). The mechanism of action of thalidomide is by inhibition of TNF-alpha secretion from leukocytes and decrease in new vessel formation (53, 54).

Our case series and the literature review showed that both TNF-alpha antagonists and thalidomide may be effective in BS patients with refractory gastrointestinal involvement.

In the EULAR recommendations for the management of BS, sulfasalazine, corticosteroids, azathioprine, TNF-alpha antagonists and thalidomide are recommended for the management of gastrointestinal involvement, except for emergencies where surgery may be required (4). In a recent consensus statement for the diagnosis and management of intestinal BS by the Japanese Research Committee for small bowel inflammation of unknown aetiology and Behçet's syndrome, infliximab and adalimumab were recommended as standard therapies for patients with severe symptoms, whereas mesalazine was recommended for patients with mild to moderate symptoms (55). Other immunosuppressives such as azathioprine are only recommended if the patients are glucocorticoid-dependent, glucocorticoid-resistant, or anti-TNF-α monoclonal antibody-resistant. Colchicine, thalidomide, other pharmacologic treatment modalities, endoscopic therapy and leukocytopheresis were accepted as experimental therapies. Both the EULAR recommendations and the Japanese consensus statement rely mostly on expert opinion and observational data rather than controlled trials.

Thalidomide was the drug of choice for refractory GIBS before TNF-alpha antagonists were available in our centre. The main problem that limits the use of thalidomide is concerns about its safety, especially regarding teratogenicity and neuropathy. In a previous randomised controlled trial with thalidomide in BS, 1 of the 32 patients who received thalidomide 100 mg/day, and 3 of the 31 patients who received 300 mg/day for 6 months developed polyneuropathy (56). Among our 6 patients who used thalidomide, 4 had clinical remission and the drug was generally well tolerated. Thus, thalidomide could still be an alternative for refractory GIBS patients who cannot use or is refractory to TNF-alpha antagonists. Concomitant use of thalidomide with infliximab may also be a favourable option. One of our patients who developed gastrointestinal involvement while using infliximab for eye involvement, obtained remission of gastrointestinal involvement when thalidomide was added.

Both our experience and the results of the literature review showed beneficial results with infliximab. Five of our 8 patients who received infliximab had remission and the literature review also showed that more than half of the patients obtained clinical remission. One of our striking observations was the rapidity of the response, starting a mean of 2 weeks after infliximab. This is very important for gastrointestinal involvement since unsuppressed inflammation can cause perforations and bleeding that may be fatal. In this line, using first-line infliximab has been tried in Crohn's disease with good results, and could be worth studying in BS patients.

Despite these promising results regarding efficacy, caution is required regarding safety with these agents. One of our 8 patients who had used infliximab and 2 of the 90 patients in the literature review had died with infectious complications. Tuberculosis that is reported to be frequent in BS patients using TNF-alpha antagonists is another challenge, since the endoscopic findings of gastrointestinal tuberculosis may be hard to distinguish from BS.

The experience with adalimumab and etanercept in GIBS is scarce, but they also seem to be effective, even in patients who were refractory to infliximab. Thus, similar to other diseases, switching from one TNF-alpha antagonist to another may be useful in Behçet's syndrome. This was also observed in a case series of 19 BS patients with different types of organ involvement (57).

Our main limitation is common to all systematic reviews on treatment of rare conditions, the tendency to publish positive results of medications in refractory cases. There are no controlled trials in GIBS and all of the data come from case reports or case series. Moreover there is no evidence to guide the dose and duration of the immunosuppressive that needs to be used before calling a patient refractory. Some clinical symptoms such as intractable abdominal pain may cause the clinician to switch to another agent early, before waiting for a sufficient time for the immunosuppressive that is being used, to work. Thus the previous medications and the baseline characteristics of the patients in our literature review were quite heterogeneous. In addition, we were not able to answer an important question, whether concomitant immunosuppressive improve the outcome of TNF-alpha antagonists. Concomitant immunosuppressive were used in less than half of the patients that were reported, but in some manuscripts concomitant medications were not reported and in some of the case series, the remission rates of patients who used and did not use immunosuppressive were not given separately.

In conclusion, our experience and limited evidence coming from case series and reports suggest favourable response with TNF-alpha antagonists and thalidomide in gastrointestinal involvement of BS, refractory to conventional treatment modalities. Switching from one of these agents to another may provide benefit when the patient is unresponsive or has a relapse under the first agent. Infectious complications may be an important challenge in BS patients using TNF-alpha antagonists. Further trials, including those addressing a step-down approach with initial TNF-alpha antagonist use and evaluating whether concomitant immunosuppressive add to the beneficial results obtained with these agents would help the development of management strategies in BS patients with gastrointestinal involvement.

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