Cerebrovascular events in inflammatory bowel disease patients treated with anti-tumour necrosis factor alpha agents

Konstantinos Karmiris, a Peter Bossuyt, b Dario Sorrentino, c Tom Moreels, d Antonella Scarcelli, e Jesus Legido, f Iris Dotan, g Graham D. Naismith, h Airi Jussila, i Jan C. Preiss, j Wolfgang Kruis, k Andy C. Y. Li, l Guillaume Bouguen, m Henit Yanai, f Flavio Steinwurz, n Konstantinos H. Katsanos, o Kayth Subramaniam, p Dino Tarabar, q IoannisV. Zaganas,r Shomron Ben-Horin, s on behalf of ECCO CONF investigators

a Department of Gastroenterology, Venizeleio General Hospital, Heraklion, Crete, Greece  
Imelda GI Clinical Research Center, Bonheiden, Belgium  
IBD Center, Virginia Tech-Carilion School of Medicine, Roanoke, VA, USA  
and Department of Clinical and Experimental Medical Sciences, University of Udine School of Medicine, Udine, Italy  
Department of Hepato-gastroenterology, Cliniques Universitaires Saint-Luc, Brussels, Belgium  
Department of Gastroenterology, Azienda University Hospital, Policlinico di Modena, Italy  
Gastroenterology Unit, Segovia General Hospital, Segovia, Spain  
IBD Center, Department of Gastroenterology and Liver Diseases and the Sackler School of Medicine, Sourasky Medical Center, Tel Aviv, Israel  
Department of Gastroenterology, Paisley RAH, Glasgow, Scotland  
Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere, Finland  
Charité-Universitätsmedizin, Berlin, Germany  
Ev. Krankenhaus Kalk, Koln, Germany  
Department of Gastroenterology, Western Sussex Hospitals NHSFT, Worthing, UK  
Department of Gastroenterology, University Hospital Pontchaillou, Rennes, France  
IBD Unit, Hospital Israelita Albert Einstein, Sao Paulo, Brazil  
Division of Gastroenterology, University Hospital of Ioannina, Greece  
Gastroenterology and Hepatology Unit, Canberra Hospital, Canberra, Australia  
Department of Gastroenterology, MMA Belgrade, Serbia  
Department of Neurology, University Hospital of Heraklion, Heraklion, Crete, Greece  
Department of Gastroenterology, Sheba Medical Center, Tel-Aviv University, Tel-Aviv, Israel

Corresponding author: Konstantinos Karmiris, MD, PhD, FEBGH, Department of Gastroenterology, Venizeleio General Hospital, Leoforos Knosou, P.O. Box 44, 71409, Crete, Greece. Tel: +30-2810-368017; fax: +30-2810-368018; Email: kkarmiris@gmail.com

Abstract

Background and aims: Cerebrovascular accidents [CVA] have rarely been reported in inflammatory bowel disease [IBD] patients treated with anti-tumour necrosis alpha [anti-TNF alpha] agents. Our aim here was to describe the clinical course of CVA in these patients.

Methods: This was a European Crohn's and Colitis Organisation [ECCO] retrospective observational study, performed as part of the CONFER [COllaborative Network For Exceptionally Rare case reports] project. A call to all ECCO members was made to report on IBD patients afflicted with CVA during treatment with anti-TNF alpha agents. Clinical data were recorded in a standardised case report form and analysed for event association with anti-TNF alpha treatment.

Results: A total of 19 patients were identified from 16 centres: 14 had Crohn's disease, four ulcerative colitis and one IBD colitis unclassified [median age at diagnosis: 38.0 years, range: 18.6–62.5]. Patients received anti-TNF alpha for a median duration of 11.8 months [range: 0–62] at CVA onset; seven had previously been treated with at least one other anti-TNF alpha agent.
Complete neurological recovery was observed in 16 patients. Anti-TNF alpha was discontinued in 16/19 patients. However, recurrent CVA or neurological deterioration was not observed in any of the 11 patients who received anti-TNF alpha after CVA [eight resumed after temporary cessation, three continued without interruption] for a median follow-up of 39.8 months [range: 5.6–98.2].

**Conclusion:** These preliminary findings do not unequivocally indicate a causal role of anti-TNF alpha in CVA complicating IBD. Resuming or continuing anti-TNF alpha in IBD patients with CVA may be feasible and safe in selected cases, but careful weighing of IBD activity versus neurological status is prudent.

**Keywords:** Cerebrovascular accidents; inflammatory bowel disease; anti-TNF alpha agents

### 1. Introduction

Inflammatory bowel disease [IBD] is considered an independent risk factor for thrombosis. Prevalence of thromboembolic events [arterial or venous thrombosis] in IBD is reported between 1.3–6.0%, with a 1.5–3.6-fold increased risk compared with the general population and other inflammatory disorders.\(^1\)\(^2\)\(^3\) This risk reaches 15-fold when referring to active IBD.\(^4\) Cerebrovascular accidents [CVA] are infrequently reported in IBD patients, mostly in the form of a single case report or small series\(^5\)\(^6\)\(^7\)\(^8\) with a reported overall prevalence of 0.12–4%.\(^2\)

Anti-tumour necrosis factor alpha [anti-TNF alpha] agents revolutionised IBD treatment. Infliximab and adalimumab are globally approved for the treatment of moderate to severe IBD.\(^9\) However, their long-term use has been associated with several neurological complications, primarily demyelinating and septic disorders.\(^10\)\(^11\) The association, if any, of anti-TNF alpha with CVA is hitherto unknown. This knowledge gap hampers the ability for rational decision making in patients who develop or are at risk of developing CVA while receiving anti-TNF alpha treatment.

We therefore set out to describe a series of IBD patients presenting with a CVA during anti-TNF alpha treatment, and to try to elucidate the impact of anti-TNF alpha resumption in these cases.

### 2. Materials and Methods

#### 2.1. Study design

This European Crohn’s and Colitis Organisation [ECCO] observational multicentre study retrospectively collected cases across the world through the CONFER [COllaborative Network For Exceptionally Rare case reports] project. The CONFER project was initiated by ECCO in order to specifically identify and report together rare IBD disease associations, which otherwise seldom get reported due to their exceptional rarity. Briefly, the CONFER methodology comprised selecting a topic worthy of investigation out of case proposals submitted by ECCO members. Once a specific IBD disease association was selected by a steering committee as a CONFER project [CVA in IBD patients under anti-TNF alpha therapy in the case of the present manuscript], ECCO launched a call to identify similar cases encountered by IBD physicians worldwide.

The call to physicians was made through announcements in the ECCO annual congress and in national IBD meetings across Europe and during two international IBD meetings [the Falk symposium in London 2013 and the Ferring symposium in Prague 2013]. In addition, the call for similar cases was disseminated by direct emails to all ECCO members and affiliated physicians and in the ECCO website and eNews. Physicians were then prompted to report their case to the CONFER database using a pre-determined standardised case report form (CRF). The call for the present case series was entitled ‘Have you encountered a case of CVA in an IBD patient associated or not with anti-TNF alpha therapy?’

#### 2.2. Patients and procedures

Adult IBD patients having a CVA while receiving anti-TNF alpha therapy were eligible for inclusion in this study. Data were collected by a CRF, which was divided into two main sections. Section 1 included patient [epidemiological data, past history] and disease (date and summary of IBD diagnosis, Montreal classification, presence and summary of extra-intestinal manifestations, anti-neutrophil cytoplasmic antibody [ANCA] or anti-Saccharomyces cerevisiae antibody [ASCA] positivity, prior IBD treatment with particular interest in duration and reason for discontinuation, and prior surgery for IBD) characteristics.

Section 2 was dedicated to description of the event. Symptoms and findings of the neurological examination were registered, including level of consciousness, speech abnormalities, visual fields defects, oculomotor disorders, abnormalities in the rest of the cranial nerves, muscle tone/strength change, presence of pyramidal or extrapyramidal signs, sensory abnormalities, signs of cerebellar deficits, gait changes, asymmetrical tendon reflexes, and urinary and/or fecal incontinence. Relevant laboratory tests as well as appropriate imaging and clinical work-up [including neuroradiological interventions] were also recorded.

CVA was defined as any ischaemic [thrombotic or embolic] or haemorrhagic [subarachnoid or intracerebral] stroke or any transient ischaemic attack.\(^12\) CVA was judged as mild, moderate, or severe according to the consulting neurologist’s decision. Event outcome was addressed at the time of report as ongoing or as having had a complete, minor, or major recovery, fatal outcome or an unknown course, again based on the neurologist’s consultation. Special interest was given to whether anti-TNF alpha therapy was discontinued due to the event and whether it was re-introduced later on. Finally, a relationship between the CVA and the above-mentioned IBD regimens or other concomitant medication or comorbidities was investigated as impossible, possible, or probable, as per the treating physician’s judgment.

All statistical analyses [frequencies, descriptive statistics, Shapiro–Wilks for normality and chi-square, Mann–Whitney test, and t-test for group comparison] were done with SPSS 20.0 software package [IBM SPSS Statistics, Armonk, NY, USA]. A \(p\)-value < 0.05 was considered statistically significant.

### 3. Results

#### 3.1. Patients’ background information

A total of 28 centres initially responded to our call. Eight CRFs were excluded either due to insufficient data [five] or not being compatible with a CVA [two] or reluctance of the patient to consent [one]. One
additional case was initially included but subsequently excluded during follow-up because the treating neurologist had severe doubts on the occurrence of a transient ischaemic attack [TIA]. Finally, 19 cases from 16 medical centres across the world were reported. Patients’ epidemiological and IBD characteristics are shown in Table 1; 17 patients were treated with at least one immunosuppressant [IMS] [either azathioprine/mercaptopurine or methotrexate] prior to CVA and all had received at least one course of corticosteroids since IBD diagnosis. The most common reason for IMS discontinuation was an adverse event in nine patients, whereas in five the treatment was still ongoing at the time of the event.

Regarding anti-TNF alpha therapy, eight patients were treated with infliximab only, four with adalimumab only, four with both agents, and three with certolizumab pegol as a third-line agent. At the onset of CVA, eight patients were receiving the anti-TNF alpha agent as monotherapy, six as combination therapy with corticosteroids, three as combination therapy with methotrexate, and two as triple combination therapy with corticosteroids and azathioprine. The duration of treatment until CVA onset was variable and averaged 11.8 ± 16.6 months [median: 5.0, range: 0.0–62.0]. More specifically, 8/19 [42.1%] were receiving anti-TNF alpha for more than 6 months before the CVA [Figure 1]. The mean [± SD] time interval between last anti-TNF alpha dose and CVA was 23.6 ± 20.9 days for infliximab and 8.4 ± 4.9 days for adalimumab. Only five patients were under an intensified anti-TNF alpha regimen at the time of the event.

3.2. CVA characteristics and outcome

CVA characteristics for the 19 patients are shown in Table 2. Symptoms and signs were diverse, with 10/19 patients presenting with hemiparesis and seven with visual disturbances. Dysarthria, numbness, perioral paraesthesia, ataxia, headache, vomiting, coordination deficits, loss of consciousness, grand mal epilepsy, and bilateral choreoathetoid movements were also reported. Complete blood count and C-reactive protein were normal in the majority of patients. Electrocardiography and Holter monitoring were normal in all patients who underwent these studies, whereas echocardiography showed patent foramen ovale in three patients. Brain computed tomographic or magnetic resonance imaging and angiography showed a seeming consequence in the form of recurrent CVA or deterioration of neurological status. Notably, this is, to our knowledge, the largest

Table 1. Demographic and clinical characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male [n]</td>
<td>9/10</td>
</tr>
<tr>
<td>Caucasian [n]</td>
<td>19</td>
</tr>
<tr>
<td>Smokers/non-smokers/ex-smokers, n = 18</td>
<td>6/7/5</td>
</tr>
<tr>
<td>CD/UC/IBDU [n]</td>
<td>14/4/1</td>
</tr>
<tr>
<td>Extra-intestinal manifestations [n]</td>
<td>9</td>
</tr>
<tr>
<td>IBD activity at CVA: active/quiescent, n = 18</td>
<td>17/19</td>
</tr>
<tr>
<td>Familial IBD history [n]</td>
<td>4 [all CD]</td>
</tr>
<tr>
<td>CD: ileitis/colitis/ileocolitis/perianal, n = 14</td>
<td>3/0/11/5</td>
</tr>
<tr>
<td>CD: B1/B2andB3, n = 14</td>
<td>9/5</td>
</tr>
<tr>
<td>UC: E1/E2/E3, n = 4</td>
<td>0/1/3</td>
</tr>
<tr>
<td>Major IBD surgeries at registration, n = 19</td>
<td>6</td>
</tr>
<tr>
<td>Mean [± SD, median] age at IBD diagnosis [years]</td>
<td>38.0 ± 14.8, 36.5</td>
</tr>
<tr>
<td>Mean [± SD, median] age at CVA onset [years]</td>
<td>47.0 ± 17.6, 48.4</td>
</tr>
<tr>
<td>Mean [± SD, median] IBD duration at CVA onset [years]</td>
<td>9.4 ± 9.5, 6.0</td>
</tr>
<tr>
<td>Mean [± SD, median] anti-TNF alpha therapy duration at CVA [months]</td>
<td>11.8 ± 16.6, 5.0</td>
</tr>
<tr>
<td>Mean [± SD, median] time interval between last anti-TNF alpha dose and CVA [days]</td>
<td>17.3 ± 17.7, 10.0</td>
</tr>
</tbody>
</table>

CD, Crohn’s disease; UC, ulcerative colitis; IBDu, inflammatory bowel disease unclassified; CVA, cerebrovascular accident; SD, standard deviation; TNF, tumour necrosis factor.

4. Discussion

The present study describes a series of IBD patients affected by a CVA while being treated with an anti-TNF alpha agent. Twelve patients had received only one anti-TNF alpha agent at the time of the event, whereas seven had received at least one other anti-TNF alpha agent before the index one, without any prior CVA. The vast majority [17/19] were also treated with an IMS either simultaneously or prior to the event. Importantly, neurological recovery was complete in 16 patients. Moreover, anti-TNF alpha was re-introduced in eight patients and continued un-interrupted in another three without any seeming consequence in the form of recurrent CVA or deterioration of neurological status. Coagulopathy tests conducted in 12 patients revealed factor V [Leiden] deficiency, hyperfibrinogenaemia, and hyperhomocysteinaemia in one patient each, whereas results were normal in nine.

CVA severity was judged as serious in 11 patients, moderate in three and mild in five. Recovery was complete in 16 patients, major in one and minor in two at last follow-up [Table 2].

IMS was discontinued in six and anti-TNF alpha was withheld in all but three patients due to the CVA. Anti-TNF alpha therapy was re-introduced at the regular dosing protocol after CVA resolution in six patients and at an intensified dosing schedule in two, and none of these patients experienced a new episode of CVA or neurological deterioration over a mean follow-up of 39.8 months [median: 37.8, range: 5.6–98.2]. Anti-TNF alpha was not re-introduced in the remaining patients due to IBD remission in two, introduction of ustekinumab in one, methotrexate-induced clinical remission in one, colectomy in one, physician’s concern regarding new central nervous system symptoms in one, and vasculitis in two for whom the biological was suspected to be the triggering factor. Relationship between the occurrence of the CVA and the IMS was judged by the treating physician as impossible in 11 patients and as possible in five, and between the CVA and the anti-TNF alpha therapy as impossible in three, as possible in 11, and as probable in five. Finally, six participants indicated a possible and two a probable relationship of the event with comorbidities.
described series of IBD patients exhibiting a CVA while receiving anti-TNF alpha therapy.

Neurological complications in IBD patients are not infrequent but are poorly recognised and under-reported. CVA are even more rare, with cerebral infarction, TIA, and cerebral venous thrombosis being most frequently reported.\textsuperscript{14,15} IBD is reported as the leading underlying condition in 1–6% of cerebral venous thrombosis incidents, in many of these cases not temporally associated with an IBD flare.\textsuperscript{15} Vasculitis, carotid arterial thrombosis, or thromboembolism, retinal branch artery occlusion, and paradoxical embolism are also reported as underlying CVA causes.\textsuperscript{16} It is unclear whether arterial or venous infarcts are more prevalent. However, cerebral arterial thrombotic events were more common in a recent population-based study.\textsuperscript{17} Our patients exhibited both venous and arterial events.

A recent meta-analysis showed that IBD is associated with an increased, albeit small, risk of CVA (odds ratio [OR] 1.18; 95% confidence interval [CI] 1.09–1.27), especially among women [OR 1.28; 95% CI 1.17–1.41] and in younger patients [< 40–50 years old].\textsuperscript{16} Another population-based nested case-control study observed an increased risk for ischaemic stroke in younger [< 50 years old; OR 2.93; 95% CI 1.44–5.98] CD patients.\textsuperscript{18} Finally, Ha et al. showed that young [< 40 years old] women with IBD exhibited an increased risk for stroke (hazard ratio [HR] = 2.1, \( p = 0.04 \)).\textsuperscript{19} Our patients were equally distributed among genders but manifested the CVA at a younger mean age [47 years] than the general population. Another population-based study indicated that a higher risk for cerebral arterial thromboembolic disease was associated only with CD (incidence rate ratio [IRR] 1.32; 95% CI, 1.05–1.66).\textsuperscript{20} This may seem to be in accordance with our group of patients, in whom the majority have had CD [14/19, 73.6%]. However, inference is impossible, as our patients were selected by anti-TNF alpha treatment, which is more commonly administered to CD patients.

Peripheral neuritis and demyelinating disorders [multiple sclerosis and optical neuritis] are the most frequently reported neurological adverse events in patients receiving anti-TNF alpha treatment.\textsuperscript{22,23} A Food and Drug Administration-supervised study reported 772 distinct neurological adverse events secondary to anti-TNF alpha agent exposure over a 10-year period.\textsuperscript{24} However, the occurrence of CVA in IBD patients receiving anti-TNF alpha agents has been scantily studied and reported.

Our case series demonstrated that CVA do occur in this subgroup of anti-TNF alpha-treated IBD patients, which warrants prompt recognition and evaluation, although the majority of our patients recovered without significant neurological sequelae. CVA occurred early after anti-TNF alpha initiation in some patients. However, this could reflect the CVA being temporally related to a more active phase of disease than to the introduction of the anti-TNF alpha agent [Figure 1]. Moreover, in 7/19 of the patients, CVA occurred after neurologically uneventful treatment with one or two other anti-TNF alpha agents prior to the index agent. Taken together with the fact that IBD itself may predispose at least to some forms of CVA, and that a proportion of patients exhibited additional risk factors for a CVA [ie smoking], the present observations may argue against a causal relation between the anti-TNF alpha agent and the CVA. Moreover, these findings could indicate that anti-TNF alpha may be safely resumed or continued in such patients, which may be important for patients who are dependent on anti-TNF alpha for IBD control. Nonetheless, these contentions should be perceived preliminarily and adopted with great caution, given the limited number of patients in this study, the retrospective nature of data collection, and the fact that the study was not designed to assess the incidence of CVA during anti-TNF alpha treatment compared with its incidence without these agents, nor whether anti-TNF alpha treatment modifies stroke incidence or severity in IBD patients. Physicians must exhibit increased vigilance when confronted with the occurrence of a CVA in an IBD patient under anti-TNF alpha therapy, and should explore further therapeutic options on a strict case-by-case basis, also keeping in mind potential non-medical consequences of their decision.

It should be noted that the outcome of CVA in our anti-TNF alpha-treated IBD patients seems no worse than the outcome of CVA in IBD patients not treated by anti-TNF alpha, based purely on clinical and imaging assessment, as described recently in a review of published case reports.\textsuperscript{14} However, there are obvious methodological caveats limiting a direct comparison. Studies in patients with rheumatoid arthritis and plaque psoriasis have produced conflicting results, either favouring the occurrence of thromboembolic events during anti-TNF alpha therapy\textsuperscript{25} or concluding that there is no correlation.\textsuperscript{26–27} Moreover, although an increase in anti-cardiolipin antibodies and possible thrombogenicity of anti-TNF alpha therapy have been proposed,\textsuperscript{26} there are conflicting mechanistic data suggesting a role for elevated TNF alpha levels in the brain during CVA as partly mediating the neuronal damage,\textsuperscript{26,28–30} thereby possibly suggesting that TNF alpha blockade may be beneficial during CVA. Elevated TNF alpha is also present in the vast majority of IBD patients, especially when the disease is active, but half of our patients were in remission when the CVA occurred, implicating a weak correlation with IBD activity. However, in the absence of population-based studies, this postulation remains at present speculative.

The limitation of the CONFER methodology should be acknowledged, as it relies on voluntary submission of cases by physicians responding to ECCO calls, which could introduce geographical and other selection biases. However, we believe this caveat is offset by the benefits of this methodology for identifying and reporting larger case series of extremely rare events, which are otherwise seldom reported other than in a single case-report format.

In conclusion, CVA affecting IBD patients treated with anti-TNF alpha agents mandates early recognition, proper work-up and specialist treatment, despite the fact that the outcome seemed to be favourable in the majority of cases in the present study. Permanent cessation of anti-TNF alpha treatment may not be universally mandatory, as continuation or resumption of the biological may be safely

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**Figure 1.** Anti-TNF alpha therapy duration [months] until CVA occurrence \([N = 19]\).
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at event [years], gender</th>
<th>IBD type and activity at event</th>
<th>CVA risk factors [other than IBD]</th>
<th>Concomitant IBD medications at event*</th>
<th>Principal imaging findings [CT or MRI]**</th>
<th>Principal symptoms [final diagnosis]</th>
<th>Event outcome</th>
<th>Event treatment</th>
<th>Anti-TNF alpha re-introduction [length of follow-up since resumption]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23, F</td>
<td>CD, active</td>
<td>None</td>
<td>ADA</td>
<td>Precentral gyrus ischaemic lesions [MRI]</td>
<td>Hemiparesis, numbness [Ischaemic CVA / ADA-induced lupus vasculitis]</td>
<td>Complete recovery</td>
<td>Methylprednisolone+ hydroxychloroquine</td>
<td>Not resumed</td>
</tr>
<tr>
<td>2</td>
<td>58, M</td>
<td>CD, quiescent</td>
<td>None</td>
<td>IFX</td>
<td>No major findings [CT]</td>
<td>Hemiparesis, visual disturbances, dysarthria [TIA]</td>
<td>Complete recovery</td>
<td>Aspirin</td>
<td>Not resumed</td>
</tr>
<tr>
<td>3</td>
<td>27, F</td>
<td>IBDU, quiescent</td>
<td>Factor V [Leiden] deficiency, current smoking</td>
<td>ADA and CS</td>
<td>Right posterior cerebral arterial embolism [CT]</td>
<td>Hemiparesis, visual disturbances, dysarthria [Ischaemic CVA]</td>
<td>Complete recovery</td>
<td>Aspirin 80 mg + phenprocoumon</td>
<td>ADA resumed 1 month later [40mg EOW], discontinued in 2012 due to lupus, CZP was introduced in 2012 and discontinued in 2013 due to haemolysis</td>
</tr>
<tr>
<td>4</td>
<td>61, F</td>
<td>CD, active</td>
<td>Current smoking</td>
<td>IFX</td>
<td>Multiple ischemic lesions [MRI]</td>
<td>Hemiparesis, visual disturbances [TIA] [Ischaemic CVA]</td>
<td>Complete recovery</td>
<td>Aspirin 100 mg</td>
<td>Not discontinued</td>
</tr>
<tr>
<td>5</td>
<td>20, M</td>
<td>CD, active</td>
<td>None</td>
<td>ADA and MTX</td>
<td>Frontal cortex ischaemic lesions [CT and MRI]</td>
<td>Hemiparesis [Ischaemic CVA]</td>
<td>Complete recovery</td>
<td>Clopidogrel</td>
<td>Not resumed</td>
</tr>
<tr>
<td>6</td>
<td>74, F</td>
<td>CD, active</td>
<td>Ischaemic heart, disease, diabetes mellitus II, former smoking</td>
<td>IFX and CS</td>
<td>Multiple periventricular ischaemic lesions [MRI]</td>
<td>Perioral paraesthesia [TIA]</td>
<td>Complete recovery</td>
<td>Aspirin</td>
<td>Not resumed</td>
</tr>
<tr>
<td>7</td>
<td>54, M</td>
<td>UC, active</td>
<td>Diabetes mellitus II, former smoking</td>
<td>IFX and AZA and CS</td>
<td>Left occipital infarction [CT]</td>
<td>Visual disturbances [Ischaemic CVA]</td>
<td>Complete recovery</td>
<td>Clopidogrel</td>
<td>Not resumed</td>
</tr>
<tr>
<td>8</td>
<td>37, M</td>
<td>CD, quiescent</td>
<td>Current smoking</td>
<td>ADA and MTX</td>
<td>Small right occipital infarct [MRI]</td>
<td>Visual disturbances, numbness [Ischaemic CVA]</td>
<td>Complete recovery</td>
<td>Warfarin</td>
<td>ADA resumed 20 days later [40mg EW]</td>
</tr>
<tr>
<td>9</td>
<td>66, F</td>
<td>CD, quiescent</td>
<td>Arterial hypertension, hypercholesterolaemia, carotid artery stenosis [50–70%], current smoking</td>
<td>ADA</td>
<td>Small marginal zone cerebral infarctions [MRI]</td>
<td>Ataxia, headache, coordination deficits [Ischaemic CVA / ADA-induced CNS vasculitis]</td>
<td>Complete recovery</td>
<td>Prednisolone + cyclophosphamide</td>
<td>Not resumed</td>
</tr>
<tr>
<td>10</td>
<td>28, F</td>
<td>UC, quiescent</td>
<td>None</td>
<td>ADA and CS</td>
<td>Sigmoid sinus thrombosis [MRI]</td>
<td>Epilepsia, loss of consciousness [Cerebral venous sinus thrombosis]</td>
<td>Major recovery</td>
<td>Heparin+phenprocoumon</td>
<td>ADA resumed 2 months later [80mg EW]</td>
</tr>
<tr>
<td>Patient</td>
<td>Age at event [years], gender</td>
<td>IBD type and activity at event</td>
<td>CVA risk factors [other than IBD]</td>
<td>Concomitant IBD medications at event*</td>
<td>Principal imaging findings [CT or MRI]**</td>
<td>Principal symptoms [final diagnosis]</td>
<td>Event outcome</td>
<td>Event treatment</td>
<td>Anti-TNF alpha re-introduction [length of follow-up since resumption]</td>
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</tr>
<tr>
<td>11</td>
<td>73, M</td>
<td>CD, quiescent</td>
<td>Arterial hypertension, former smoking</td>
<td>IFX</td>
<td>Bilateral cerebral ischaemic lesions [MRI]</td>
<td>Aphasia, bilateral choreoathetoid movements, chronic choreoathetosis [Ischaemic CVA]</td>
<td>Minor recovery</td>
<td>Clopidogrel</td>
<td>Not resumed</td>
</tr>
<tr>
<td>12</td>
<td>48, M</td>
<td>CD, active</td>
<td>None</td>
<td>IFX and CS</td>
<td>No major findings [CT]</td>
<td>Hemiparesis, dysarthria [Ischaemic CVA]</td>
<td>Complete recovery</td>
<td>Clopidogrel</td>
<td>ADA resumed 1.5 month later [40 mg EOW]</td>
</tr>
<tr>
<td>13</td>
<td>36, F</td>
<td>CD, active</td>
<td>None</td>
<td>IFX and CS</td>
<td>Right middle cerebral artery occlusion with basal ganglia involvement [CT]</td>
<td>Hemiparesis, numbness, dysarthria [Ischaemic CVA]</td>
<td>Complete recovery</td>
<td>Mechanical thrombectomy + aspirin</td>
<td>ADA resumed 2.5 years later after ileocecectomy [40 mg EOW]</td>
</tr>
<tr>
<td>14</td>
<td>59, M</td>
<td>CD, quiescent</td>
<td>Current smoking</td>
<td>IFX and AZA and CS</td>
<td>No major findings [CT and MRI]</td>
<td>Visual disturbances, dysarthria [TIA]</td>
<td>Complete recovery</td>
<td>Aspirin 100 mg</td>
<td>Not discontinued</td>
</tr>
<tr>
<td>15</td>
<td>43, F</td>
<td>CD, quiescent</td>
<td>Current smoking</td>
<td>IFX</td>
<td>Sigmoid and transverse sinus thrombosis [MRI]</td>
<td>Headache and vomiting [Cerebral venous sinus thrombosis]</td>
<td>Complete recovery</td>
<td>Aspirin 100 mg</td>
<td>ADA resumed 1 month later [40 mg EOW]</td>
</tr>
<tr>
<td>16</td>
<td>45, F</td>
<td>CD, active</td>
<td>None</td>
<td>ADA</td>
<td>Sagittal sinus thrombosis [MRI]</td>
<td>Headache, dizziness, temporary loss of consciousness [Cerebral venous sinus thrombosis]</td>
<td>Complete recovery</td>
<td>Aspirin 100 mg</td>
<td>ADA resumed 1.5 month later [40 mg EOW]</td>
</tr>
<tr>
<td>17</td>
<td>63, M</td>
<td>UC, quiescent</td>
<td>Former smoking</td>
<td>ADA</td>
<td>Left sylvian ischaemic lesions [MRI]</td>
<td>Hemiparesis, dysarthria [Ischaemic CVA]</td>
<td>Minor recovery</td>
<td>Aspirin 80 mg</td>
<td>Not discontinued</td>
</tr>
<tr>
<td>18</td>
<td>21, M</td>
<td>UC, active</td>
<td>None</td>
<td>IFX and CS</td>
<td>Cerebral and right pons infarct [MRI]</td>
<td>Hemiparesis, visual disturbances, loss of consciousness [Ischaemic CVA]</td>
<td>Minor recovery</td>
<td>Aspirin + warfarin</td>
<td>Not resumed</td>
</tr>
<tr>
<td>19</td>
<td>56, M</td>
<td>CD, quiescent</td>
<td>Former smoking</td>
<td>IFX and MTX</td>
<td>Internal carotid ectasias [MR angiography]</td>
<td>Hemiparesis, dysarthria, aphasia, loss of consciousness [TIA]</td>
<td>Complete recovery</td>
<td>Clopidogrel for 6 months IFX resumed 2.5 months later [5 mg/kg]</td>
<td></td>
</tr>
</tbody>
</table>

CD, Crohn’s disease; UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified; CVA, cerebrovascular accident; SD, standard deviation; TNF, tumour necrosis factor; ADA, adalimumab; AZA, azathioprine; CS, corticosteroids; IFX, infliximab; MTX, methotrexate; MRI, magnetic resonance imaging; CT, computed tomography; TIA, transient ischaemic attack; CNS, central nervous system; EW, each week; EOW, every other week; CZP, certolizumab pegol.
practised in some patients. However, until further data are available, this needs to be a case-by-case decision after careful weighing of the neurological state as well as the disease activity and risk for IBD complications in the individual patient.

**Potential conflicts of interest**

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**Specific author contributions**

KK conceived the study, analysed and interpreted the data and drafted the manuscript; PB, DS, TM, AS, JL, ID, GDN, AJ, JCP, WK, ACYL, GB, HY, FS, KHK, KS, and DT contributed the cases and critically revised the manuscript; IVZ participated in study design and disease specific risk factor for thromboembolism? Gut 2004;53:342–8.


