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ORIGINAL ARTICLE

Infliximab versus Cyclophosphamide for Severe Behçet's Syndrome

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Abstract

BACKGROUND Cyclophosphamide and infliximab are recommended as induction therapies for severe Behçet's syndrome. Whether infliximab is safer and more effective than cyclophosphamide in treating severe Behçet's syndrome is not known.

METHODS In this phase 2, Bayesian, multicenter randomized controlled trial, we assigned patients fulfilling the International Study Group's criteria for Behçet's syndrome who had major vascular or central nervous system involvement to receive either intravenous infliximab (5 mg/kg at weeks 0, 2, 6, 12, and 18) or cyclophosphamide (0.7 g/m^2 intravenously at weeks 0, 4, 8, 12, 16, and 20, with a maximal dose of 1.2 g/infusion). All patients received the same glucocorticoid regimen. The primary outcome was complete response (clinical, biological, and radiological remission with a daily prednisone dose ≤0.1 mg/kg) at week 22.

RESULTS Between May 2018 and April 2021, 52 patients with severe Behçet's syndrome (n=37 [71%] with vascular Behçet's syndrome and n=15 [29%] with neuro-Behçet's syndrome) were randomly assigned to receive either infliximab or cyclophosphamide. Complete response was achieved by 22 out of 27 (81%) and 14 out of 25 (56%) patients in the infliximab and cyclophosphamide treatment groups, respectively (estimated difference, 29.8 percentage points; 95% credible interval, 6.6 to 51.7). The posterior probability that at least 70% of treated individuals achieved complete response by week 22 was 97.4% for infliximab and 6.0% for cyclophosphamide. Overall, adverse events were recorded in 8 out of 27 (29.6%) patients receiving infliximab and 16 out of 25 (64%) patients receiving cyclophosphamide (estimated difference, −32.3 percentage points; 95% credible interval, −55.2 to −6.6). Serious adverse events were reported in 15% and 12% of patients receiving infliximab and cyclophosphamide, respectively.

CONCLUSIONS Among patients with severe Behçet's syndrome, induction therapy with infliximab had a superior complete response rate at 22 weeks and fewer adverse events than induction with cyclophosphamide. (Funded by the French Ministry of Health.)

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Introduction

Behçet's syndrome is a chronic multisystem inflammatory condition that runs a relapsing–remitting course[1] and may involve the skin, mucosa, joints, eyes, arteries, veins, central nervous system (CNS), and gastrointestinal system. Behçet's syndrome increases the rate of morbidity and mortality, especially among young male individuals and those with severe disease defined by vascular manifestations (i.e., vascular Behçet's) and neurological involvement (i.e., neuro-Behçet's).[2] Vascular Behçet's may affect both veins and arteries of all calibers, and it is the main cause of mortality among people with Behçet's syndrome, mostly due to arterial aneurysms or Budd–Chiari syndrome.[2,3] Among people with neuro-Behçet's, rates of severe disability or death reach 25% at 7 years.[4,5] Although the burden of severe Behçet's syndrome is substantial, the therapeutic strategies in this context have only been assessed in observational studies.[6]

Cyclophosphamide and glucocorticoids have long been the standard remission-induction therapy for severe Behçet's syndrome.[6] Cyclophosphamide has been prescribed in life-threatening vascular and neurological Behçet's manifestations with some efficacy in retrospective studies.[4,7-10] However, disease flares requiring repeated treatment courses may lead to high cumulative doses of both drugs over time. The short- and long-term adverse events (AEs) of cyclophosphamide use in Behçet's syndrome are substantial[9] and add to the known side effects of glucocorticoids, further increasing overall rates of treatment-related morbidity. These important safety concerns highlight the need for safer and more efficient remission-induction strategies in severe Behçet's syndrome.

Tumor necrosis factor alpha (TNFα) is an important proinflammatory cytokine implicated in Behçet's pathogenesis.[11] Infliximab, a monoclonal TNFα inhibitor, has been the most studied TNFα inhibitor in severe Behçet's syndrome. TNFα inhibitors have been successful in eliciting high response rates in severe and refractory Behçet's syndrome in retrospective series[6,12-14] and have also been associated with decreased blindness in Behçet's syndrome uveitis.[15] These data suggest infliximab may be a promising agent for the treatment of severe Behçet's syndrome and raise the question of whether it should be used earlier in Behçet's syndrome management.

Current international guidelines recommend the use of high-dose glucocorticoids combined with either cyclophosphamide or TNFα inhibitors as induction therapy for severe vascular and neuro-Behçet's syndrome.[16] Because such recommendations are based on uncontrolled evidence, the optimal therapeutic strategy in this setting remains unclear. We conducted the Induction Therapy with Anti-TNFα versus Cyclophosphamide trial, a multicenter randomized controlled trial aiming to evaluate whether infliximab improved complete response rates at 22 weeks in patients with severe Behçet's syndrome compared with cyclophosphamide.

Methods

TRIAL DESIGN AND OVERSIGHT

This phase 2, multicenter, open-label randomized controlled trial was conducted in 21 centers across France within the French Behçet's Network. The protocol was approved by the Comité de Protection des Personnes Sud-Est VI (reference number 2017-002264-41). All patients or their legally authorized representative provided written informed consent. The trial was conducted in accordance with the Declaration of Helsinki and was registered on ClinicalTrials.gov (NCT03371095). The trial protocol included an observational period of up to 3 years. The reporting of this trial conforms to the Consolidated Standards of Reporting Trials (CONSORT) statement.[17]

TRIAL POPULATION

Patients 12 years of age or older who fulfilled the International Study Group's criteria for Behçet's syndrome,[18] with either major vascular (i.e., arterial aneurysms, stenosis or occlusion, and/or major deep vein thrombosis) or CNS involvement (i.e., encephalitis, meningoencephalitis, or myelitis) were eligible for inclusion. International Study Group criteria and exclusion criteria are further detailed in the Supplementary Methods in the Supplementary Appendix. Eligible patients had active disease at the time of enrollment, defined as the appearance of major vascular and/or CNS manifestations of Behçet's syndrome, associated with a typical radiological presentation and/or biological inflammatory markers (both described below). The vascular and neurological systems are the major organs involved in Behçet's syndrome morbidity and mortality, and their involvement is herein considered the criterion for severe Behçet's syndrome.

INTERVENTION AND RANDOMIZATION

Eligible patients were randomly assigned 1:1 to receive either infliximab (5 mg/kg intravenously at weeks 0, 2, 6,

12, and 18) or cyclophosphamide (0.7 g/m^2 intravenously at weeks 0, 4, 8, 12, 16, and 20, with a maximal dose of 1.2 g/infusion). Premedication consisted of paracetamol and dexchlorpheniramine for infliximab, and ondansetron and uromitexan for cyclophosphamide (Supplementary Methods in the Supplementary Appendix). All participants received the same glucocorticoid regimen as standard of care, that is, an oral prednisone equivalent 1 mg/kg/day (up to 80 mg/day). Glucocorticoids were tapered beginning at week 4 according to a prespecified schedule (Supplementary Methods in the Supplementary Appendix) as long as the severe Behçet's syndrome did not present clinical, biological, and/or radiological worsening, with a goal of attaining a dosage ≤0.1 mg/kg/day by week 22. The treatment administration schedule for infliximab and cyclophosphamide adhered to the recommended dosage guidelines for rheumatic diseases.[16] There were no specific considerations for pediatric patients beyond weight-based dosing; all patients received proper management and precautions associated with the administration of these medications. Participants were evaluated at every intravenous infusion and additionally at weeks 12 and 22 by trial investigators who collected clinical and laboratory data for efficacy and safety assessments. Complementary imaging examinations (i.e., computed tomography angiography [CTA], magnetic resonance angiography [MRA], vascular Doppler ultrasound, or CNS magnetic resonance imaging [MRI]) were obtained at baseline as well as at weeks 12 and 22. All collected data were registered in an electronic database and further validated by the trial coordinating staff.

Randomization was stratified by baseline major vascular or CNS involvement and according to newly diagnosed or relapsing Behçet's syndrome status. The electronic randomization scheme was centralized to ensure allocation concealment.

OUTCOMES

The primary outcome was a complete response at week 22, defined as resolution of all baseline vascular Behçet's syndrome or neuro-Behçet's syndrome clinical manifestations, normalization of C-reactive protein (CRP) levels, and radiological remission while on a prednisone dosage ≤0.1 mg/kg/day. Specifically, vascular remission required the absence of new lesions in previously unaffected vascular territories and the absence of progression of preexisting vascular lesions detected on serial imaging studies (i.e., vascular Doppler ultrasound, CTA, or MRA). Neurological remission required the absence of contrast-enhanced CNS lesions on MRI and the absence of physical neurological sequelae, defined by a modified Rankin Scale score <1 (range 0–6; higher scores indicate more severe disability, minimal clinically important difference ≥1).[19] The main secondary outcomes included complete response rates at week 12; specific remission rates of CNS and vascular involvement at weeks 12 and 22; and remission rates of other Behçet's syndrome manifestations at weeks 12 and 22. Exploratory secondary outcomes included median glucocorticoid dose and the percentage of patients achieving prednisone dosages ≤0.1 mg/kg/day at week 22; mean changes from baseline in CRP level at week 22; changes from baseline in Behçet's Disease Current Activity Form index score (range 0–12; higher scores for each component indicate higher disease activity) and Physician's Global Assessment score (based on a visual-analog scale ranging from 0 to 100 mm; higher scores indicate greater disease activity) at weeks 12 and 22; quality-of-life changes from baseline at weeks 12 and 22 according to physical and mental scores from the 36-Item Short-Form Health Survey (SF-36; range 0–100; higher scores represent better function); relapse rates by week 22; and frequency and severity of AEs at week 22.

Remission definitions regarding other Behçet's syndrome features are detailed in the Supplementary Methods in the Supplementary Appendix. Relapses were defined as the new occurrence or reappearance following remission of clinical and/or radiological features of active disease. Severe AEs were those requiring hospitalization or resulting in death.

An external End-Point Adjudication Committee blinded to the randomization reviewed the vascular and neurological imaging end points collected throughout the trial.

STATISTICAL ANALYSIS

This trial was designed as a Bayesian phase 2 randomized clinical trial that aimed to evaluate treatment strategies for severe Behçet's syndrome, based on the difference in the response rate as measured at week 22 after randomization. We used the approach for phase 2 randomized trials proposed by Simon, Wittes, and Ellenberg[20] that aims to control the probability of detecting a given difference in response rates. In this approach, the drugs are ranked based on the differences in the observed response rates between the randomly assigned treatment groups; sample size can be determined by considering an expected baseline value, sometimes called the "minimum required treatment response rate" for sample size determination, which was set at 0.70 in this trial, and the expected difference between treatment groups, set at 0.15. Using Bayesian inference, we computed for each treatment group the probability π

that the response rate was above 0.70, P(π>0.7), based on previous response rates to cyclophosphamide of 70% in severe, vascular, or neurological Behçet's syndrome,[7,10] as additional probabilistic information on the response rate. We used a noninformative beta-binomial model for π with a prior beta(1,1) and an informative prior beta(7,3) established by the clinicians at the time of conception of the trial as an alternative analysis based on the abovementioned literature. Primary outcomes (overall complete response at week 22) and main secondary outcomes (overall complete response at week 12, vascular complete response at weeks 12 and 22, CNS complete response at weeks 12 and 22) were analyzed as mentioned above. Differences between treatment groups were assessed with the use of the median and the 95% credible interval (CrI) of the posterior distribution. Other exploratory binary secondary outcomes were analyzed similarly. For secondary quantitative outcomes, differences between groups were assessed with the use of means differences and the 95% CrIs of their posterior distribution. We used a noninformative normal distribution as prior N(μ=0, σ=1000).

We hypothesized that up to 70% of patients receiving cyclophosphamide and 85% of those treated by infliximab would achieve a complete remission of Behcet's syndrome at 22 weeks and with ≤0.1 mg/kg/day of prednisone. Thus, based on binomial distributions for the number of responses under the assumed response rate of the baseline cyclophosphamide treatment group (here, P=0.70), this allowed us to randomly assign two groups of 27 and 25 patients each in order for the better treatment to rank first in terms of response rate to detect with a 0.90 probability, assuming a 0.15 difference in response rates between the treatment groups. Patients were assessed in the treatment group to which they were randomly assigned (intent-to-treat analysis) to avoid treatment selection biases in the estimation of treatment effect.

Continuous variables were summarized as medians and interquartile ranges, and categorical variables as counts and percentages. Statistical analysis was performed using R software (R version 4.0.4).

Results

CHARACTERISTICS OF TRIAL POPULATION

Between May 2018 and April 2021, 52 patients with Behçet's syndrome were enrolled (median age 39.4 years, 57.7% male). Three pediatric patients were included (two 14-year-old patients and one 15-year-old patient); all were randomly assigned to receive infliximab. The baseline characteristics of included patients are presented in Table 1. The trial sample was generally representative of patients with Behçet's syndrome, with a higher prevalence of male patients, in line with established knowledge that vascular and neurological manifestations in Behçet's syndrome tend to occur more frequently in men.[1] Additional background information on Behçet's syndrome demographics and the representativeness of our patient sample is presented in Table S1. Across both trial treatment groups, 39 patients (75.0%) had been recently diagnosed. Major vascular and CNS involvement was present in 37 (71.1%) and 15 (28.9%) patients, respectively. Deep venous thrombosis (40.4%), arterial aneurysms (28.8%), and arterial thrombosis (25.0%) were the most prevalent vascular manifestations. Headache (26.9%), motor deficit (19.2%), meningitis (15.4%), and ataxia (11.5%) were the most frequent symptoms in patients with CNS involvement, and the median Rankin Scale score was 1 (interquartile range, 1 to 2.5). At the time of inclusion, about half of the overall population had other concomitant Behçet's syndrome clinical features (Table 1). The mean CRP serum level was 7 mg/l (±6.7) and 13.1 mg/l (±25) in patients receiving cyclophosphamide and infliximab, respectively. The median Behçet's Disease Current Activity Form index score was 3 (interquartile range, 2 to 4), and the median Physician's Global Assessment score was 60 (interquartile range, 40.5 to 80.0) The median values for SF-36 physical and mental domains were 41.3 (interquartile range, 27.7 to 58.8) and 47.8 (interquartile range, 35.9 to 63.7), respectively.

Figure 1 displays patients' assignment to trial groups and reasons for treatment discontinuation. Twenty-seven patients were randomly assigned to the infliximab group and 25 patients were assigned to cyclophosphamide (median cumulative dose of 7.2 g; interquartile range, 6.7 to 7.2). Treatment groups were balanced with respect to their baseline features, notably regarding major organ involvement (i.e., vascular vs. CNS) and newly diagnosed status.

PRIMARY OUTCOME

Complete response at week 22 was reached by 22 out of 27 (81%) patients in the infliximab group compared with 14 out of 25 (56%) patients receiving cyclophosphamide, with an estimated difference of 29.8 percentage points (95% CrI, 6.6 to 51.7) (Table 2). The posterior probability that 70% of patients would achieve complete response by week 22 was 97.4% for infliximab and 6.0% for cyclophosphamide

Table 1. Baseline Characteristics of Trial Patients.*

Variable	Cyclophosphamide (n=25)	Infliximab (n=27)	SMD
Age, years	40.9 [34.7 to 48.2]	38.1 [29.3 to 46.0]	0.40
12–35	7 (28)	9 (33)	
36–45	9 (36)	10 (37)	
>45	9 (36)	8 (30)	
Age at diagnosis, years	35.2 [32 to 47.6]	35.4 [25.1 to 41.1]	0.38
Female sex	10 (40)	12 (44)	0.09
Behçet's syndrome newly diagnosed at enrollment	19 (76)	20 (74)	0.05
Major vascular involvement	18 (72)	19 (70)	0.04
Arterial aneurysm	8 (32)	7 (26)	0.13
Arterial thrombosis or stenosis	10 (40)	3 (11)	0.70
Deep venous thrombosis	10 (40)	11 (41)	0.02
CNS involvement	7 (28)	8 (30)	0.04
Brainstem lesions	4 (16)	4 (15)	0.03
Supratentorial lesions	2 (8)	5 (18)	0.31
Myelitis	0	3 (11)	0.50
Cerebral thrombophlebitis	1 (4)	1 (4)	0.02
Other concomitant Behçet's syndrome manifestations			
Cutaneous lesions	14 (56)	11 (41)	0.31
Oral ulcers	14 (56)	9 (33)	0.47
Genital ulcers	4 (16)	5 (18)	0.07
Arthralgia	3 (12)	4 (15)	0.08
Uveitis	0	3 (11)	0.5
Behçet's syndrome assessment scores			
Behçet's Disease Current Activity Form index	2 [2 to 3]	3 [1 to 4]	0.17
Physician's Global Assessment	70 [50.0 to 80.0]	60 [40.2 to 77.5]	0.19
Mean CRP level, mg/l (±SD)	7 (±6.7)	13.1 (±25)	0.33
Previous treatments			
Glucocorticoids	10 (40)	14 (52)	0.24
Colchicine	4 (16)	5 (18)	0.07
Synthetic immunosuppressants	4 (16)	4 (15)	0.03

*Categorical data are presented as n (%), whereas quantitative data are reported as median [interquartile range]. The Behçet's Disease Current Activity Form index ranges from 0 to 12, with higher scores for each component indicating higher activity. The Physician's Global Assessment was assessed on the basis of a visual-analog scale ranging from 0 to 100 mm, with higher scores indicating greater disease activity. A normal value for CRP is below 3 mg/l. Deep venous thrombosis included pulmonary (n=9), suprahepatic (n=7), and vena caval (n=6). Cutaneous lesions comprised papulopustular acneiform lesions (n=14), pathergy reaction (n=5), erythema nodosum (n=1), and pseudofolliculitis (n=1). Uveitis comprised panuveitis (n=2) and posterior uveitis (n=1). Gastrointestinal involvement and peripheral arthritis were not present in any patient at inclusion. Synthetic immunosuppressants comprised azathioprine (n=7) and azathioprine and mycophenolate mofetil (n=1). CNS, central nervous system; CRP, C-reactive protein; SD, standard deviation; and SMD denotes standardized mean difference.

using a non-informative prior beta(1,1) (Fig. 2). Results were similar using an informative prior beta(7,3) in alternative analyses (Table S2 and Fig. S1).

Overall, the primary outcome was met by 36 (69%) patients, including 27 out of 37 (73%) with major vascular involvement and 9 out of 15 (60%) with CNS involvement (Table S3).

SECONDARY OUTCOMES

Secondary outcomes are summarized in Table 2 and Table S5. By week 12, overall complete response was observed in 17 out of 27 (65%) and 16 out of 25 (64%) patients in the infliximab and cyclophosphamide treatment groups, respectively. By week 22, 17 out of 19 (94%) and 10 out of 18 (56%) patients achieved complete response of

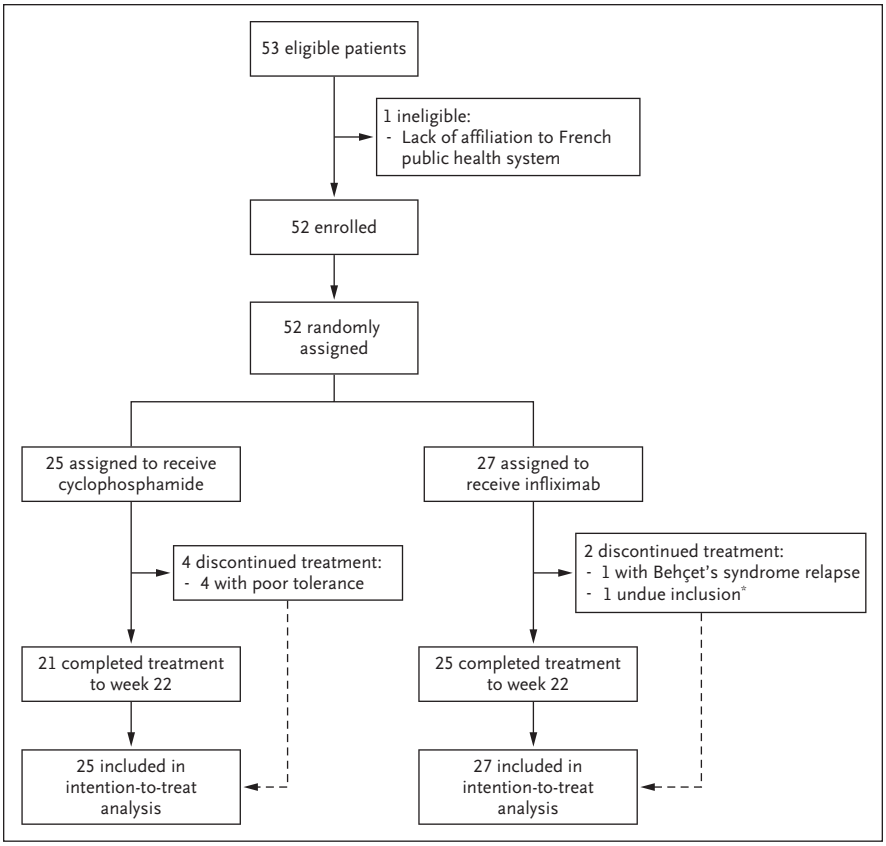

Figure 1. Trial Flowchart.

Fifty-three patients were assessed for eligibility. One patient was not enrolled due to their lack of affiliation to the French public health system. Out of the 52 patients who were enrolled, 25 patients were randomly assigned to the cyclophosphamide treatment group and 27 patients to the infliximab treatment group. Randomization was stratified according to the main Behçet's syndrome involvement at baseline (i.e., major vascular or CNS involvement), and to the newly diagnosed (vs. relapsing) status. All but six patients completed the 22 weeks of treatment (week 22) to which they were assigned. The reasons for treatment discontinuation were poor tolerance (n=4) in the cyclophosphamide treatment group, and Behçet's syndrome relapse (n=1) and undue inclusion (n=1) in the infliximab treatment group. *The latter had his participation withdrawn by the investigator by week 12 once control imaging studies of a peripheral arterial aneurysm had put into question Behçet's syndrome as the cause of such vascular involvement. Data related to trial's outcomes were available for all patients and were analyzed on an intention-to-treat basis. CNS denotes central nervous system.

vascular involvement in the infliximab and cyclophosphamide groups, respectively (estimated difference: 35.2 percentage points; 95% CrI, 9.7 to 59.2). By week 22, 5 out of 8 (71%) and 4 out of 7 (57%) patients receiving infliximab and cyclophosphamide achieved complete response of CNS involvement, respectively (estimated difference: 11.4 percentage points; 95% CrI, −31.9 to 52.3). Regarding other Behçet's syndrome manifestations, both groups experienced clinical improvement over time, with no differences between treatments (Table S6). A glucocorticoid dosage of less than 0.1 mg/kg/day at week 22 was achieved by 95.8% and 92% of patients within infliximab and cyclophosphamide groups, respectively (Fig. S2). Relapse occurred in one (4%) patient receiving infliximab and four (16%) patients receiving cyclophosphamide (estimated difference: −12.3 percentage points; 95% CrI, −29.6 to 4.8).

At week 22, treatment with infliximab was associated with a lower mean CRP serum level than treatment with cyclophosphamide (mean values±SD, 4.0±5.4 vs. 9.4±12.3 mg/l, respectively; estimated difference −5.3 mg/l; 95% CrI, −10.6 to −0.1). Overall, both treatments were associated with an approximately 2-point reduction in Behçet's Disease Current Activity Form index scores over time, with no apparent differences between treatments (Fig. S3). The same trend toward improvement occurred for both treatment groups regarding Physician's Global Assessment scores. The quality-of-life assessments using SF-36 were consistent

Table 2. Primary and Secondary Outcomes at Week 22.*

Outcomes	Cyclophosphamide (n=25)	Infliximab (n=27)	Estimated difference (95% CrI)
Primary Outcome			
Overall complete response	14/25 (56)	22/27 (81)	29.8 (6.6 to 51.7)
Main Secondary Outcomes			
Vascular complete response	10/18 (56)	17/19 (94)	35.2 (9.7 to 59.2)
CNS complete response	4/7 (57)	5/8 (71)	11.4 (−31.9 to 52.3)
Relapse	4 (16)	1 (4)	−12.3 (−29.6 to 4.8)
Exploratory Secondary Outcomes			
No. of patients receiving prednisone ≤0.1 mg/kg/day	23/25 (92)	23/24 (96)	3.2 (−12.2 to 19.5)
Median prednisone doses (mg/d)	8 [5 to 8]	7 [5 to 8.3]	−0.5 (−2.1 to 1.2)
Mean CRP level, mg/l	9.4 (±12.3)	4.0 (±5.4)	−5.3 (−10.6 to −0.1)
Behçet's Disease Current Activity Form index	0 [0 to 1]	0 [0 to 1]	−0.1 (−0.6 to 0.3)
Physician's Global Assessment	10 [1.8 to 23.8]	10 [3.8 to 20]	−2.7 (−15.5 to 10)
SF-36 physical scores	41 [29 to 66.7]	56 [34.4 to 67.7]	3.8 (−12.8to 20.5)
SF-36 mental scores	57.8 [37.4 to 75.9]	58.92 [35.2 to 72.3]	3.2 (−14 to 20.4)
No. of patients with AEs	16 (64)	8 (30)	−32.3 (−55.2 to −6.6)
No. of patients with serious AEs	3 (12)	4 (14.8)	2.5 (−16.8 to 21.5)

*Trial's outcomes are presented as the estimated treatments' difference for week 22. Categorical data are presented as n (%), and quantitative data as median [interquartile range] or mean (±standard deviation). All analyses were performed using a prespecified Bayesian approach for which estimated differences are reported along their 95% CrI. For the primary outcome, we used a noninformative prior beta(1,1), and an informative beta(7,3) as an alternative analysis. The Behçet's Disease Current Activity Form index ranges from 0 to 12, with higher scores for each component indicating higher activity. The Physician's Global Assessment was assessed on the basis of a visual-analog scale ranging from 0 to 100 mm, with higher scores indicating greater disease activity. Quality of life was assessed according to the physical and mental domain scores of the SF-36, each one ranging from 0 to 100, with higher scores representing better function. AE denotes adverse event; CNS, central nervous system; CrI, credible interval; and SF-36, 36-Item Short-Form Health Survey.

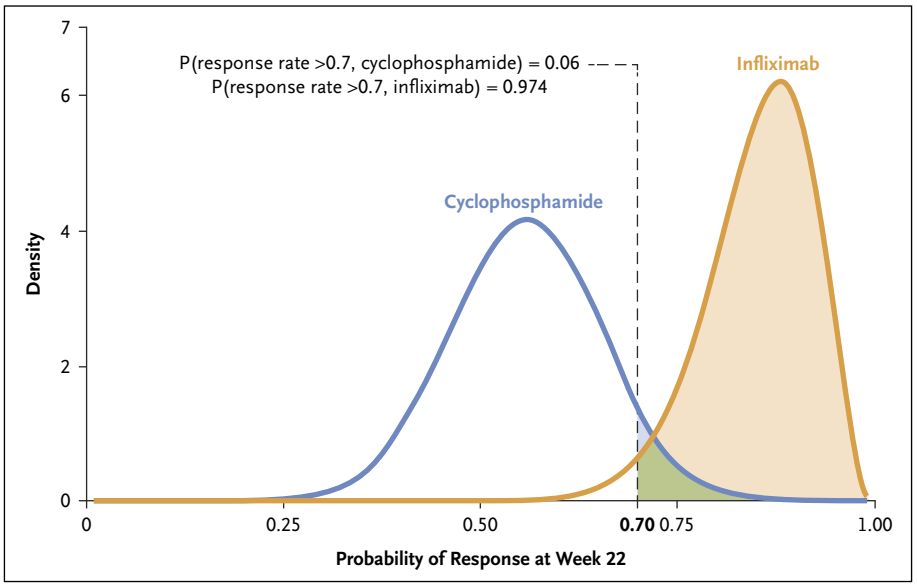

Figure 2. Posterior Probability of the Difference in Complete Response Rates at Week 22.

The posterior probabilities with a prior beta(1,1) are provided. The response rate in the infliximab treatment group was greater than that in the cyclophosphamide treatment group, with a 95% CrI ranging from 0.066 to 0.517. CrI denotes credible interval.

with improvements in physical and mental domains in both treatment groups (Fig. S5).

ADVERSE EVENTS

The frequency and severity of AEs that occurred through week 22 are shown in Table 3. Mild-to-moderate AEs were recorded in 8 out of 27 (29.6%) and 16 out of 25 (64%) patients in the infliximab and cyclophosphamide groups, respectively (estimated difference, −32.3 percentage points; 95% CrI, −55.2 to −6.6). These included mainly infections (23.1%, n=12) managed in the outpatient setting. Other mild-to-moderate AEs included gastrointestinal intolerance and alopecia for cyclophosphamide, and infusion-related reactions for infliximab. Serious AEs requiring hospitalizations occurred in 7 out of 52 (13.4%) patients and were mainly due to infections, with no apparent difference between groups. No deaths were recorded. Four out of 25 (16%) patients discontinued cyclophosphamide before the last trial dose due to poor tolerance; 2 out of 27 (7.4%) patients discontinued infliximab, due to Behçet's relapse for one patient and participation withdrawal for the second (Fig. 1).

Discussion

This randomized, head-to-head trial provides evidence for infliximab's superiority over cyclophosphamide in induction of remission of severe Behçet's syndrome (i.e., vascular and neurological), with a complete response achieved in 81% of patients receiving infliximab versus 56% of those receiving cyclophosphamide. Furthermore, the posterior probability of achieving a response of 70% in each group was 97.4% for infliximab and 6.0% for cyclophosphamide.

Table 3. Adverse Events in Overall Trial Population and According to Intervention Treatment Group.*

	Cyclophosphamide (n=25)	Infliximab (n=27)	Total (n=52)
Any mild-to-moderate AE	16 (64)	8 (30)	24 (46)
Total no. of mild-to-moderate AEs	29	13	42
Mild-to-moderate infections	6 (24)	6 (22)	12 (23)
Pulmonary	3	2	5
Genitourinary	0	2	2
Viral infection	0	2	2
Other†	3	0	3
Other mild-to-moderate AEs	19 (76)	7 (26)	26 (50)
Nausea and vomiting	7	2	9
Alopecia	5	0	5
Infusion related‡	1	2	3
Elevated liver enzymes	2	0	2
Asthenia	2	0	2
Autoimmune reactions§	0	2	2
Anemia	0	1	1
Mucositis	1	0	1
Diarrhea	1	0	1
Any severe AE	3 (12)	4 (15)	7 (13)
Total no. of severe AEs	4	5	9
Sepsis	0	3	3
Cutaneous abscess	2	0	2
Pneumonia	1	1	2
Covid-19	1	0	1
Gastroenteritis	0	1	1

* Categorical data are presented as n (%). AE denotes adverse event; and Covid-19, coronavirus disease 2019.
† Other mild-to-moderate infections included asymptomatic Covid-19, a dental infection, and furunculosis.
‡ Infusion-related AEs comprised headache (n=2 for the infliximab treatment group) and treatment extravasation (n=1 for the cyclophosphamide treatment group).
§ Autoimmune reactions occurring in the infliximab treatment group were psoriasiform skin lesions (n=1) and mild drug-induced lupus (n=1).

Infliximab was also associated with greater benefit than cyclophosphamide in some of the secondary outcomes. First, the infliximab group was associated with lower relapse rates than the cyclophosphamide group. Next, when splitting complete response according to major organ manifestation, infliximab was associated with a greater complete response rate than cyclophosphamide in vascular Behçet's syndrome (94% for infliximab vs. 56% for cyclophosphamide; see Table 2) and neuro-Behçet's syndrome (71% vs. 57%; see Table 2). Infliximab has been successfully administered in severe and refractory Behçet's syndrome.[12,16,22] In a Turkish study evaluating the appearance of new Behçet's syndrome manifestations under infliximab, only 20 out of 282 (7%) patients developed new manifestations; most of these were managed without the need for treatment discontinuation.[13] Finally, the infliximab group was associated with lower CRP levels at week 22 than the cyclophosphamide group.

For decades, cyclophosphamide has been a cornerstone of treatment for severe Behçet's syndrome. However, its superiority over surgery or other immunosuppressant treatments in vascular Behçet's syndrome has mostly been documented in small retrospective studies evaluating pulmonary artery involvement.[14] In neuro-Behçet's syndrome, the efficacy of cyclophosphamide is controversial.[21] In the largest retrospective study evaluating long-term outcomes in patients with neuro-Behçet's syndrome, no statistical difference between cyclophosphamide, azathioprine, and glucocorticoids alone was observed regarding the overall event-free survival (i.e., no relapse or death).[4] This finding might reflect substantial bias, since cyclophosphamide is usually prescribed for patients with more severe disease. Among patients with severe neuro-Behçet's syndrome (Rankin Scale score ≥3 at onset), cyclophosphamide tended to yield higher event-free survival than azathioprine.[4] TNF-α is reported to play a pivotal role in Behçet's syndrome inflammation, with consistently elevated levels in the sera and target tissues in patients with Behçet's syndrome.[11,22] Emerging data on TNFα inhibitors have been changing paradigms in severe Behçet's syndrome, notably in Behçet's syndrome uveitis patients, in which they have been proposed as first-line agents.[12,15,16,23] In severe vascular Behçet's syndrome, pooled retrospective data from 126 patients receiving TNFα inhibitors yielded effectiveness rates higher than 80%.[24] Even higher rates were reported by small series of patients with refractory neuro-Behçet's syndrome, with very few relapses following TNFα inhibitors.[25,26]

Cyclophosphamide is an alkylating agent that affects several cell lines; its toxicity can derive from its cumulative dose, which can be particularly consequential for young patients with Behçet's syndrome. Cyclophosphamide safety was assessed in a large Turkish cohort of patients with Behçet's syndrome between 1976 and 2006, for whom vascular and neurological involvements comprised about 70% of treatment indications.[9] Overall, 9% of patients had short-term AEs (mainly hemorrhagic cystitis), and 8% experienced malignancies over the long term. Infertility was estimated at 30%. In our trial, patients receiving cyclophosphamide had more mild-to-moderate AEs than those in the infliximab group (64.0% vs. 29.6%, respectively). Most AEs in the cyclophosphamide treatment group were gastrointestinal and infectious. No clear differences concerning serious AEs or infections were observed between groups. In severe Behçet's syndrome, TNFα inhibitors' safety has been previously evaluated among 124 patients from a large multicenter cohort, which found an overall side effect rate of 28% after a median of 21 months, mostly infections.[12]

Our trial has limitations. The randomized open-label design is susceptible to a performance bias. However, using objective outcomes assessments (i.e., imaging) evaluated by an independent committee should guard against this. Another limitation is the small number of patients with neuro-Behçet's syndrome (n=15), which is in line with the low prevalence of neurological involvement in Behçet's syndrome. Thus, our results should be interpreted with caution in this subgroup. Finally, the heterogeneous nature of the clinical manifestations of Behçet's syndrome might have an impact on treatment outcomes.

In conclusion, the findings of this phase 2 trial suggest the superior efficacy of infliximab over cyclophosphamide for induction of remission in patients with severe Behçet's syndrome.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

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