Effectiveness of SB5, an Adalimumab Biosimilar, in Patients With Noninfectious Uveitis: A Real-Life Monocentric Experience

Jurgen Sota, MD, Stefano Gentileschi, MD*, Antonio Vitale*, Carla Gaggiano, MD*†, Giuseppe De Bartolo‡, Maria Teresa Bianco§, Bruno Frediani, MD*, Gian Marco Tosi, MD, PhD‡, Luca Cantarini, MD, PhD*, and Claudia Fabiani, MD, PhD‡*

Purpose: Several concerns have arisen with biosimilars in terms of immunogenicity, safety issues, loss of efficacy, and extrapolation to other indications. The study aim was to evaluate the efficacy of SB5, an adalimumab biosimilar, in noninfectious uveitis (NIU).

Design: Retrospective nonrandomized study.

Methods: Data from patients with refractory NIU treated with SB5 (Imraldi, Biogen) were analyzed at baseline, 3 months after SB5 initiation and at the last follow-up in terms of uveitis relapses, occurrence of retinal vasculitis, resolution of uveitic macular edema (UME), best-corrected visual acuity, glucocorticoids (GCs)-sparing effect and drug survival.

Results: Uveitis relapses decreased from 121 relapses/100 patients/year in the 12 months before SB5 initiation to 4 relapses/100 patients/year during the first 12 months of treatment ($P = 0.0004$). Uveitis was inactive in 46/47 eyes at the end of the study period. The number of eyes with active retinal vasculitis decreased during the study period ($P < 0.0001$). At baseline, 6 eyes presented UME, whereas no eye had UME at the last follow-up. Mean best-corrected visual acuity increased from 7.7 ± 3.41 at baseline to 8.9 ± 2.46 at the last follow-up ($P = 0.0045$). Mean GCs daily dosage decreased from 18.33 ± 10.33 mg at baseline to 5.75 ± 2.29 mg at the last follow-up ($P = 0.018$). The cumulative SB5 retention rate was 91.8% at both 12- and 20-month follow-up.

Conclusions: SB5 biosimilar is effective in NIU by drastically reducing uveitis relapses and the occurrence of retinal vasculitis. Moreover, SB5 biosimilar improved visual acuity, allowed a significant GCs-sparing effect and showed an excellent drug retention rate.

Key Words: adalimumab biosimilar, SB5, uveitis

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From the *Department of Medical Sciences, Surgery and Neurosciences, Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinic, University of Siena, Siena, Italy; †Clinical Pediatrics, Department of Molecular Medicine and Development, University of Siena, Siena, Italy; ‡Department of Medicine, Ophthalmology Unit, Surgery and Neuroscience, University of Siena, Siena, Italy; and §Pharmacy Unit, Siena University Hospital 'Santa Maria alle Scotte', Siena, Italy.

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Address correspondence and reprint requests to: Luca Cantarini, Department of Medical Sciences, Surgery and Neurosciences, Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinic, University of Siena, Siena, Italy. E-mail: cantariniluca@hotmail.com.

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INTRODUCTION

Uveitis is a leading cause of preventable blindness in developed countries and its impact on patients' quality of life goes beyond the influence on visual acuity alone.[1,2] This high-morbidity condition carries an elevated socioeconomic burden given its substantial impact among working-age adults.[3] Early treatment constitutes therefore a crucial step for an optimal management of this sight-threatening condition. Although glucocorticoids (GCs) represent the gold standard of treatment in the acute phase, complications arising as a consequence of their both systemic and local long-term usage have highlighted the need for the use of steroid-sparing agents, such as conventional and biotechnological disease-modifying antirheumatic drugs.[4–6] Several studies have provided the rationale for the use of biologic response modifiers.[7–11] In this regard, Adalimumab (ADA), a genetically engineered fully humanized IgG1 monoclonal antibody binding with high affinity to tumor necrosis factor (TNF)-α,[12] has proved its efficacy in achieving or maintaining quiescence and in reducing GCs burden in several clinical trials.[13,14] As a result, ADA is currently the only nonsteroid treatment licensed for the management of noninfectious uveitis (NIU).[15] ADA effectiveness has been later corroborated in a real-life setting.[16–24]

After the recent expiration of the original patent protection, a number of ADA biosimilar products have been approved for use in Europe.[25] Their development has raised some concerns in terms of potential immunogenicity, safety issues, loss of efficacy, and development of antidrug antibodies.[26,27] Moreover, extrapolation to other indications remains an issue as rheumatoid arthritis may not guarantee a sensitive model that is able to detect potential differences between biosimilar and originator products.[28,29] SB5 (Imraldi®, Biogen), developed as a biosimilar referencing ADA, has demonstrated an equivalent clinical efficacy and safety profile in patients with rheumatoid arthritis.[30] On the contrary, data regarding its efficacy in NIU on both biologic-naïve patients and those switching from the originator are scarce and these aspects represent understudied areas. We herein provide our monocentric experience with patients affected by NIU and treated with SB5.

METHODS

Population and Design

Medical charts of patients suffering from NIU and treated with SB5 were retrieved and retrospectively analyzed. Patients were treated with SB5 between December 2018 and August 2020.

Before SB5 initiation, biologic-naïve patients underwent x-ray chest examination, tuberculin protein purified derivate skin testing and/or QuantiFERON test, liver markers for HBV and HCV infections, and urine culture in order to rule out any active or latent infection. Exclusion criteria were pregnancy and New York Heart Association functional classes III and IV. Patients diagnosed with oncologic conditions within the last 5 years before SB5 initiation were also excluded from the study. Patients were regularly evaluated every 3 months or in case of necessity (safety concerns and/or disease relapse).

Data Collection

The following demographic, clinical and therapeutic data were collected for statistical purposes: sex, age, age at uveitis onset, uveitic disease duration, systemic diagnosis related to uveitis, characterization of major histocompatibility complex, previous and concomitant treatment with conventional immunosuppressants and GCs, and previous biologic therapies. Ophthalmological work-up included classification of uveitis according to the Standardization of Uveitis Nomenclature criteria,[31] laterality of uveitis, number of uveitis relapses in the 12 months preceding SB5 initiation and during follow-up, best-corrected visual acuity (BCVA), detection of retinal vasculitis and uveitic macular edema (UME), and/or further ocular complications occurring while on SB5 treatment. BCVA was measured with Snellen chart in decimal fractions at any follow-up visit. The diagnosis of UME and active retinal vasculitis was based on clinical, optical coherence tomography, and fluoroangiographic findings.

Aims and Endpoints

The primary aim of the study was to evaluate SB5 efficacy in terms of uveitic relapses. Secondary aims addressed the following issues: resolution of retinal vasculitis, impact of SB5 on visual acuity, the influence on GCs daily intake, its overall survival in the cohort, and ocular complications and safety profile.

Primary endpoints consisted in evaluating potential statistical differences between the number of uveitis relapses between the 12 months before SB5 initiation and those encountered during follow-up. Secondary endpoints assessed at baseline, 3 months, and the last follow-up visit were: resolution of active retinal vasculitis; UME resolution; changes in BCVA; variations in the mean GCs (prednisone or equivalent) daily dosage administered at baseline and at the last follow-up visit; Kaplan–Meier curves for the overall SB5 drug retention rate; description of ocular complications and any systemic adverse event occurring during SB5 treatment.

The study protocol conformed to the tenets of the Declaration of Helsinki and received approval by the local Ethics Committee of the Azienda Ospedaliera Universitaria Senese (Reference No. 14951). Informed consent was obtained from each patient or their legal guardian.

Statistics

Data were computed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY). Descriptive statistics was used to calculate percentage, mean and standard deviation, or median and interquartile range, as appropriate. Shapiro-Wilk test was employed to assess data normality distribution. Multiple repeated categorical measures were analyzed with Cochran Q test followed by McNemar test with Bonferroni correction for post-hoc analysis.

Wilcoxon signed-rank test and Mann–Whitney U test were used for the analysis of ordinal and continuous variables, as required. Cumulative survival rate was studied by Kaplan–Meier plot with the event being the drug discontinuation. The threshold for statistical significance was set to $P < 0.05$ and all P values were 2-sided.

RESULTS

Twenty-six patients (47 eyes) treated with SB5, of whom 15 were females, were enrolled in the study. The median ± interquartile range treatment duration was 16.50 ± 6.00 months (range 14 months). Uveitis was unilateral and bilateral in 5 and 21 cases, respectively. Main demographic and therapeutic characteristics of our cohort are summarized in Table 1. The anatomical pattern of uveitis was anterior in 12 eyes, posterior in 10 eyes, and panuveitis in 25 eyes. Twenty-two patients started biologic treatment because of active uveitis, whereas the remaining 4 were treated with SB5 due to uncontrolled systemic disease. Three patients were not treated with the standard regimen of 40 mg every other week. More in detail, 2 of them received 40 mg every week and the other one 40 mg every 10 days. Behçet syndrome represented the most frequently encountered systemic disorder (n = 8), followed by spondyloarthritis (n = 5), Vogt-Koyanagi-Harada syndrome (n = 2), enteropathic arthritis

TABLE 1. Demographic, Clinical, and Therapeutic Features of the Cohort Enrolled

Patients (no.)	26
Sex (F/M)	15/11
HLA	HLA-B27 (n = 7) HLA-B51 (n = 7)
Age, y (mean ± SD)	43.50 ± 15.14
Age at uveitis onset, y (median ± IQR)	33.50 ± 14.50
Uveitis duration, y (median ± IQR)	3.00 ± 15.50
Laterality	Bilateral ($n = 21$) Unilateral ($n = 5$)
Anatomical pattern of uveitis (no. eyes)	Anterior uveitis ($n = 12$) Posterior uveitis ($n = 10$) Panuveitis ($n = 25$)
Associated systemic disease	Behçet syndrome ($n = 8$) Spondyloarthritis ($n = 5$) Entheropatic arthritis ($n = 2$) Vogt-Koyanagi-Harada ($n = 2$) Sarcoidosis ($n = 1$)
Concomitant treatment with cDMARDs	Methotrexate ($n = 1$) Cyclosporine A ($n = 1$) Azathioprine ($n = 3$)
Previous treatment with cDMARDs	Methotrexate ($n = 6$) Cyclosporine A ($n = 4$) Azathioprine ($n = 1$) Sulfasalazine ($n = 5$) Micofenolate mofetil ($n = 1$) Thalidomide ($n = 1$)
Previous biologic agents	Adalimumab originator (n = 18) Infliximab (n = 3) Etanercept (n = 3) Anakinra (n = 3)

cDMARDs indicates conventional disease modifying antirheumatic drugs; IQR, interquartile range; SD, standard deviation.

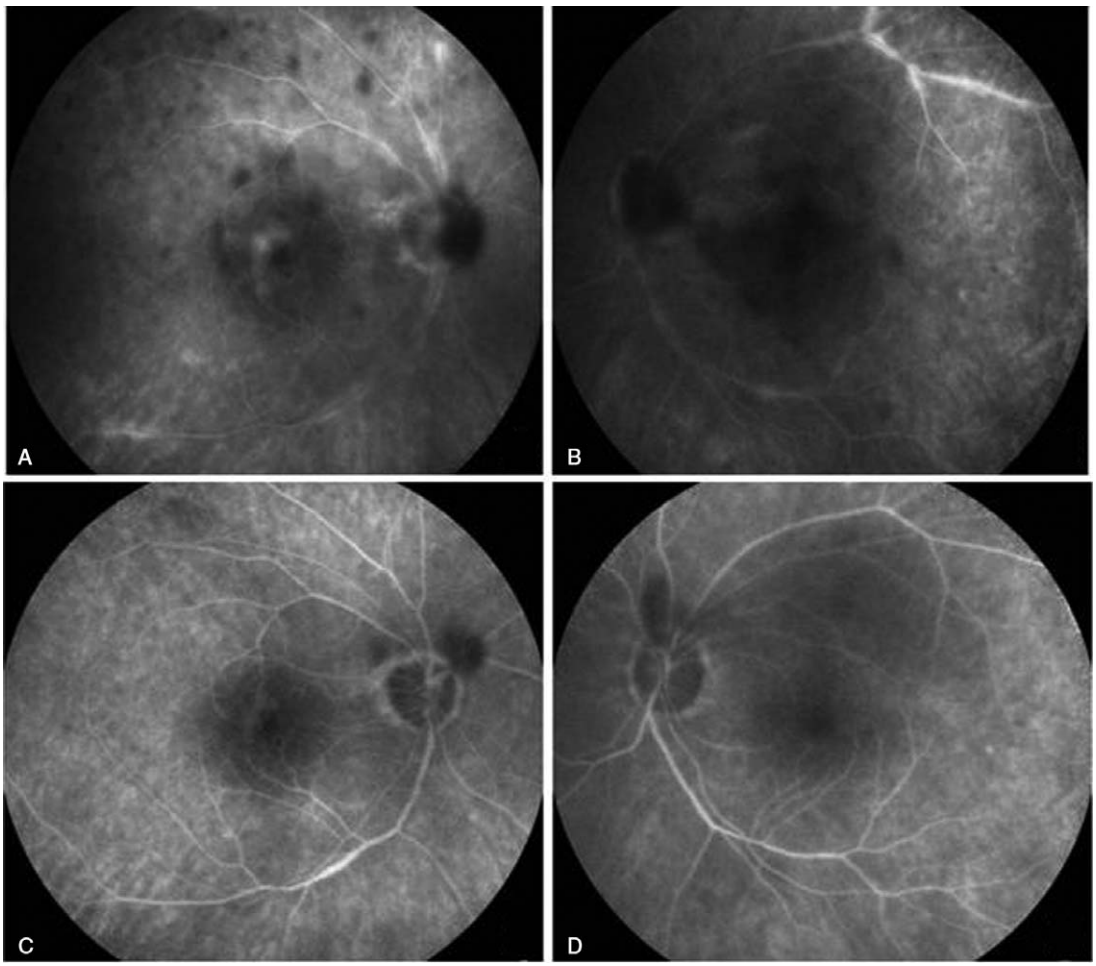

FIGURE 1. Fluorescein angiography findings in a patients affected by bilateral idiopathic panuveitis. Upper images show late-phase angiograms disclosing an active posterior pole retinal vasculitis and the presence of macular edema in the right eye (A) and an active posterior pole retinal vasculitis in the left eye (B), at baseline. Lower images show late-phase angiograms disclosing resolution of posterior pole retinal vasculitis and macular edema in the right eye (C) and resolution of posterior pole vasculitis in the left eye (D), after treatment with SB5 biosimilar agent administered subcutaneously every 2 weeks.

(n = 2), and sarcoidosis (n = 1) whereas 8 patients had idiopathic uveitis.

The number of uveitis relapses decreased from 121 relapses/100 patients/year in the 12 months before the start of SB5 to 4 relapses/100 patients/year during the first 12 months of treatment ($P = 0.0004$) and from 115 relapses/100 patients/year to 3 relapses/100 patients/year at the last follow-up ($P < 0.0001$). Uveitis was inactive in 46 of 47 eyes at the last follow-up.

The number of eyes affected by active retinal vasculitis significantly decreased during the study period ($P < 0.0001$). Post-hoc analysis revealed a significant decrease from baseline to 3 months ($P = 0.019$) and from baseline to 12 months ($P = 0.0007$). Figure 1 shows the resolution of retinal vasculitis in a patient with idiopathic panuveitis after treatment with SB5 biosimilar. At the end of the study period, 1 patient (2 eyes) showed no resolution of retinal vasculitis. At baseline, 6 eyes presented UME, whereas no eye had UME at the last follow-up. Table 2 provides data regarding ocular findings at baseline (SB5 initiation) and at the end of the study period. Mean BCVA increased from 7.7 ± 3.41 at baseline to 8.9 ± 2.46 at the last follow-up ($P = 0.0045$). Mean GCs' daily dosage decreased from 18.33 ± 10.33 mg at baseline to 5.75 ± 2.29 mg at the last follow-up visit, displaying a statistically significant difference ($P = 0.018$). At the end of the study, 2 subjects had discontinued

TABLE 2. Ocular Findings Associated With Uveitis at the Moment of SB5 Initiation and at the Last Follow-up Assessment

	Ocular Findings at SB5 Initiation		Ocular Findings at Study End	
	RE	LE	RE	LE
RV (no. eyes)	9	7	1	1
CME (no. eyes)	3	3	0	0
BCVA (mean ± SD)	7.64 ± 3.69	7.34 ± 3.51	8.89 ± 2.54	8.95 ± 2.44

BCVA indicates best-corrected visual acuity; CME, cystoid macular edema; FA, fluorescein angiography; LE, left eye; RE, right eye; RV, retinal vasculitis; SB5, adalimumab biosimilar; SD, standard deviation.

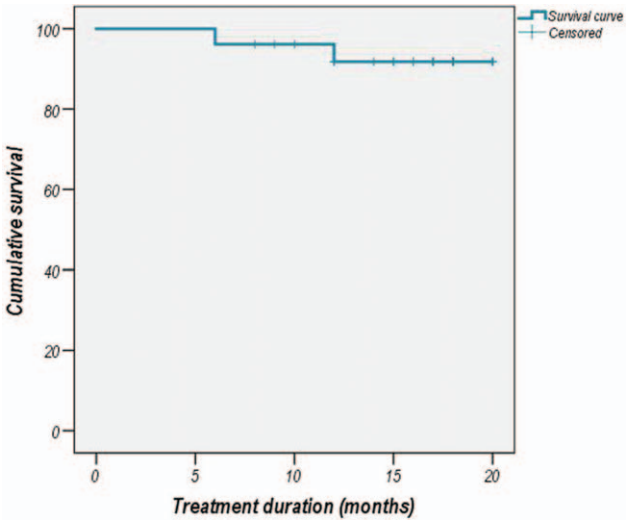

FIGURE 2. Overall SB5 Retention Rate of Our Cohort During Follow-up.

SB5 treatment, one due to a prostatic carcinoma diagnosed after 6 months of biologic therapy and the other one due to loss of efficacy. One patient experienced an injection site reaction which was classified as a mild adverse event. Figure 2 illustrates the overall SB5 retention rate during the study period. In detail, the estimated cumulative SB5 retention rate at 12- and 20-month follow-up visits was equal to 91.8% at both selected time points. No new ocular complications emerged during the treatment with SB5 biosimilar.

DISCUSSION

In this retrospective case series, we investigated the potential role of SB5 as a biologic treatment for the treatment of NIU, either idiopathic or associated with systemic inflammatory disorders. The goal of NIU treatment is to control ocular inflammation thus preventing the onset of severe long-term ocular complication and visual function impairment, while minimizing treatment-related side-effects.[32] NIU causes serious consequences in terms of morbidity and negatively impacts on patients' quality of life thus demanding a rich therapeutic armamentarium which is essential to manage refractory cases.[2] The need for GCs-sparing agents has heralded the development of therapies modulating specific cytokine pathways. More in detail, with the advent of biologic agents and specifically anti-TNF-α agents, the therapeutic landscape of uveitis has experienced a substantial revolution. ADA has proven to be highly effective,[16–24] and recent evidence suggests that also other TNF-α inhibitors,[33,34] anti-interleukin-1,[35,36] and anti-interleukin-6[37–39] may represent alternative options in difficult-to-handle cases.

SB5 and its referenced original compound product have been shown to be highly similar with regard to their pharmacokinetic effects and biologic characteristics,[40,41] supported by clinical evidence as well.[30] However, several concerns have arisen with biosimilars in terms of immunogenicity, safety issues, loss of efficacy, development of antidrug antibodies, and extrapolation to other indications.[26–29]

Our findings suggest a notable efficacy of SB5 in the management of NIU in terms of preventing uveitis relapses. In particular, uveitis relapses decreased from 115 relapses/100 patients/year in the 12 months before the start of SB5 to 3 relapses/100 patients/year during the follow-up period. Moreover, in our series uveitis was inactive in 97.8% of affected eyes at the last follow-up. SB5 biosimilar seems therefore able both to control intraocular inflammation and to maintain quiescence in most patients with NIU. Comparable results have been reported in randomized clinical trials[13] and in real-life studies,[42] showing a significant reduction in uveitis relapses. In their sample of 82 patients, Al-Janabi et al[42] found a shorter time to response in patients treated with ADA along with a longer time to failure.

With regard to retinal vasculitis, a remarkable improvement in the number of affected eye was observed at 3- and 12-months follow-up visits compared to baseline. Similar results have been reported in a cohort of patients affected by retinal vasculitis and treated with the reference products of infliximab and ADA.[16] Other articles as well have reported a rapid efficacy of TNF-α monoclonal antibodies in resolving retinal vasculitis, either idiopathic or associated with systemic immune-mediated diseases.[43–45]

As for BCVA improvement and the mean GCs' daily intake, in line with previous studies reporting encouraging results of the reference product,[22,46] SB5 biosimilar proved to preserve and even improve visual acuity while significantly reducing GCs burden and its long-term liabilities. Concerning drug survival, SB5 disclosed a comparable drug retention rate with previous reports with estimated values of roughly 90% at 12 months. Similarly, Llorenç et al reported a drug retention rate of 87.86% at 12-month follow-up in patients treated with ADA originator[19,23] The absence of new ocular complications emerging during treatment with SB5 further supports its efficacy in managing this sight-threatening condition.

Altogether, the findings discussed above should be carefully interpreted, given the retrospective design of our study with its inherited drawbacks alongside the relatively small sample size and the lack of a control group.

In conclusion, SB5 biosimilar is effective for the treatment of NIU, either idiopathic or associated with systemic inflammatory diseases, by controlling uveitis relapses, drastically reducing the occurrence of retinal vasculitis, and improving visual acuity. Moreover, SB5 shows an excellent drug retention rate with a significant GCs-sparing effect. In this context, SB5 biosimilar may be a reliable additional weapon in the growing therapeutic armamentarium available for NIU.

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