

**COMPARATIVE STUDY OF INFLIXIMAB VERSUS  
 ADALIMUMAB IN REFRACTORY UVEITIS DUE TO BEHÇET'S  
 DISEASE. NATIONAL MULTICENTER STUDY OF 177 CASES**

Journal:	<i>Arthritis &amp; Rheumatology</i>
Manuscript ID	ar-18-1234.R2
Wiley - Manuscript type:	Full Length
Date Submitted by the Author:	11-Jun-2019
Complete List of Authors:	<p>Atienza-Mateo, Belén ; Hospital Universitario Marqués de Valdecilla. IDIVAL, Rheumatology          Martín-Varillas, José Luis; Hospital Universitario Marqués de Valdecilla. IDIVAL, Rheumatology          Calvo-Río, Vanesa; Hospital Universitario Marqués de Valdecilla. IDIVAL, Rheumatology          Demetrio-Pablo , Rosalia; Hospital Universitario Marqués de Valdecilla. IDIVAL, Ophthalmology          Beltrán, Emma; Hospital del Mar, Rheumatology          Sanchez-Burson, Juan; Hospital de Valme, Rheumatology          Mesquida, Marina; Hospital Clinic, Ophthalmology          Adan, Alfredo; Hospital Clinic, Rheumatology          Hernandez, Maria Victoria; Hospital Clinic, Rheumatology          Hernandez-Grafella, Marisa; Consorci Hospital General Universitari de Valencia, Ophthalmology          Valls Pascual, Elia; Hospital Universitario Doctor Peset, Rheumatology          Martínez-Costa, Lucía; Hospital Universitario Doctor Peset, Ophthalmology          Sellas-Fernández, Agustí; Hospital Vall d'Hebron, Rheumatology          Cordero-Coma, Miguel; Hospital de Leon, Ophthalmology          Díaz-Llopis, Manuel; Hospital Universitario La Fe, Ophthalmology          Gallego-Pinzano, Roberto; Hospital Universitario La Fe, Ophthalmology          García-Serrano, José L.; Hospital Universitario San Cecilio, Ophthalmology          Ortego-Centeno, Norberto; Hospital Clínico Universitario San Cecilio, Unit of Systemic Autoimmune Diseases          Herreras, José M.; Hospital Universitario, IOBA, Ophthalmology          Fonollosa, Alejandro; Hospital de Cruces, Ophthalmology          APARICIO, ANGEL; Hospital Provincial de Toledo, Rheumatology          Maíz-Alonso, Olga; Hospital Universitario de Donostia, Rheumatology          Blanco, Ana; Hospital Universitario de Donostia, Ophthalmology          Torre, Ignacio; Hospital Universitario de Basurto, Rheumatology          Fernández-Espartero, Cruz; Hospital Universitario de Móstoles, Rheumatology          Jovani, Vega; Hospital General Universitari d'Alacant, Rheumatology          PEITEADO, DIANA; Hospital Universitario La Paz, Rheumatology          Pato, Esperanza; Hospital Clínico San Carlos, Rheumatology          Cruz, Juan; Complejo Hospitalario de Pontevedra, Rheumatology          Fernández-Cid, Carlos; Complejo Hospitalario de Pontevedra,</p>

	<p>Ophthalmology</p> <p>Aurrecochea, Elena; Hospital Sierrallana, Rheumatology</p> <p>García, Miriam; Hospital Universitario de la Princesa, Rheumatology</p> <p>Castañeda, Santos; Hospital Universitario de la Princesa, Rheumatology</p> <p>Caracuel, Miguel A.; Hospital de Córdoba, Rheumatology</p> <p>Montilla, Carlos; Hospital Clínico de Salamanca, Rheumatology</p> <p>Atanes, Antonio; Complejo Hospitalario Universitario A Coruna, Rheumatology</p> <p>Francisco, Felix; Hospital Doctor Negrín, Rheumatology</p> <p>Insua, Santos; Hospital Universitario Santiago de Compostela, Rheumatology</p> <p>González-Suárez, Senen; Hospital Cabueñes, Rheumatology</p> <p>Sanchez-Andrade, Amalia; Hospital Universitario Lucus Augusti, Rheumatology</p> <p>Gamero, Fernando; Hospital San Pedro Alcantara, Rheumatology</p> <p>Linares, Luis; Hospital Clinico Universitario Virgen de la Arrixaca, Rheumatology</p> <p>Romero, Fredeswinda; Fundación Jiménez Díaz, Rheumatology</p> <p>García-González, A. Javier; Hospital Universitario 12 de Octubre, Rheumatology</p> <p>Raquel, Almodovar; Hospital Universitario Fundacion Alcorcon, Rheumatology</p> <p>Minguez, Enrique; Hospital Clínico de Zaragoza, Ophthalmology</p> <p>Carrasco-Cubero, Carmen; Hospital Universitario Infanta Cristina, Rheumatology</p> <p>Olivé, Alejandro; Hospital Universitari Germans Trias i Pujol, Rheumatology</p> <p>Prior-Español, Águeda; Hospital Universitari Germans Trias i Pujol, Rheumatology</p> <p>Vázuquez, Julio; Hospital de Ferrol, Rheumatology</p> <p>Ruiz Moreno, Oscar; Hospital Universitario Miguel Servet, Ophthalmology</p> <p>Jiménez-Zorzo, Fernando; Hospital Universitario Miguel Servet, Rheumatology</p> <p>Manero, Javier; Hospital Universitario Miguel Servet, Rheumatology</p> <p>Muñoz-Fernández, Santiago; Hospital Universitario Infanta Sofía, Rheumatology</p> <p>Fernández-Carballido, Cristina; Hospital General Universitario de Elda, Rheumatology</p> <p>Rubio Romero, Esteban; Hospital Universitario Virgen del Rocio, Rheumatology</p> <p>Pages, Fred Anton; Hospital Universitario Virgen del Rocio, Rheumatology</p> <p>Toyos-Sáenz de Miera, Francisco J.; Hospital Virgen de la Macarena, Rheumatology</p> <p>Gandia, Myriam; Hospital Universitario Puerta del Mar, Rheumatology</p> <p>Diaz-Valle, David; Hospital Clínico San Carlos, , Ophthalmology</p> <p>López-Longo, Francisco; Hospital Universitario de Mostoles, Rheumatology</p> <p>Nolla, Joan Miquel; Hospital Universitari de Bellvitge, Rheumatology</p> <p>Raya, Enrique; Hospital Universitario San Cecilio, Rheumatology</p> <p>Revenga, Marcelino; Hospital Universitario Ramon y Cajal, Rheumatology</p> <p>González-López, Julio; Hospital Universitario Ramón y Cajal, Ophthalmology</p> <p>Rodríguez-Cundin, Paz; Hospital Universitario Marqués de Valdecilla. IDIVAL, Preventive Medicine</p> <p>Hernandez, Jose; Hospital Universitario Marqués de Valdecilla. IDIVAL, Internal Medicine</p> <p>Gonzalez-Gay, Miguel; Hospital Universitario Marqués de Valdecilla. IDIVAL, Rheumatology</p> <p>Blanco, Ricardo; Hospital Universitario Marqués de Valdecilla. IDIVAL, Rheumatology</p>
--	---

Keywords:	uveitis, Behçet-s Syndrome, Infliximab, adalimumab, multicenter study
<b>&lt;B&gt;Disease Category&lt;/b&gt;:</b> Please select the category from the list below that best describes the content of your manuscript.:	Behçet's Syndrome

SCHOLARONE™  
Manuscripts

**COMPARATIVE STUDY OF INFLIXIMAB VERSUS ADALIMUMAB IN  
REFRACTORY UVEITIS DUE TO BEHÇET'S DISEASE. NATIONAL MULTICENTER  
STUDY OF 177 CASES**

Belén Atienza-Mateo, MD,<sup>1</sup> José Luis Martín-Varillas, MD,<sup>1</sup> Vanesa Calvo-Río, MD, PhD,<sup>1</sup> Rosalía Demetrio-Pablo, MD, PhD,<sup>1</sup> Emma Beltrán, MD,<sup>2</sup> Juan Sánchez-Bursón, MD, PhD,<sup>3</sup> Marina Mesquida, MD, PhD,<sup>4</sup> Alfredo Adan, MD, PhD,<sup>4</sup> María Victoria Hernández, MD,<sup>4</sup> Marisa Hernández-Garfella, MD,<sup>5</sup> Elia Valls-Pascual, MD,<sup>6</sup> Lucía Martínez-Costa, MD, PhD,<sup>6</sup> Agustí Sellas-Fernández, MD,<sup>7</sup> Miguel Cordero-Coma, MD, PhD,<sup>8</sup> Manuel Díaz-Llopis, MD, PhD,<sup>9</sup> Roberto Gallego, MD, PhD,<sup>9</sup> José L. García-Serrano, MD, PhD,<sup>10</sup> Norberto Ortego-Centeno, MD, PhD,<sup>11</sup> José M. Herreras, MD, PhD,<sup>12</sup> Alejandro Fonollosa, MD, PhD,<sup>13</sup> Ángel M. Garcia-Aparicio, MD,<sup>14</sup> Olga Maíz-Alonso, MD,<sup>15</sup> Ana Blanco, MD,<sup>15</sup> Ignacio Torre-Salaberri, MD,<sup>16</sup> Cruz Fernandez-Espartero, MD,<sup>17</sup> Vega Jovaní, MD, PhD,<sup>18</sup> Diana Peiteado, MD, PhD,<sup>19</sup> Esperanza Pato, MD,<sup>20</sup> Juan Cruz, MD,<sup>21</sup> Carlos Fernández-Cid, MD,<sup>22</sup> Elena Aurrecochea, MD, PhD,<sup>23</sup> Miriam García-Arias, MD,<sup>24</sup> Santos Castañeda, MD, PhD,<sup>24</sup> Miguel A. Caracuel-Ruiz, MD, PhD,<sup>25</sup> Carlos A. Montilla-Morales, MD, PhD,<sup>26</sup> Antonio Atanes-Sandoval, MD, PhD,<sup>27</sup> Félix Francisco, MD,<sup>28</sup> Santos Insua, MD,<sup>29</sup> Senen González-Suárez, MD,<sup>30</sup> Amalia Sanchez-Andrade, MD, PhD,<sup>31</sup> Fernando Gamero, MD,<sup>32</sup> Luis F. Linares Ferrando, MD, PhD,<sup>33</sup> Fredeswinda Romero-Bueno, MD, PhD,<sup>34</sup> A. Javier García-González, MD,<sup>35</sup> Raquel Almodóvar González, MD,<sup>36</sup> Enrique Minguez Muro, MD, PhD,<sup>37</sup> Carmen Carrasco-Cubero, MD,<sup>38</sup> Alejandro Olive, MD, PhD,<sup>39</sup> Águeda Prior, MD,<sup>39</sup> Julio Vázquez, MD,<sup>40</sup> Oscar Ruiz-Moreno, MD, PhD,<sup>41</sup> Fernando Jiménez-Zorzo, MD,<sup>41</sup> Javier Manero, MD,<sup>41</sup> Santiago Muñoz Fernandez, MD, PhD,<sup>42</sup> Cristina Fernández-Carballido, MD, PhD,<sup>43</sup> Esteban Rubio-Romero, MD,<sup>44</sup> Fred Antón Pages, MD,<sup>44</sup> Francisco J. Toyos-Sáenz de Miera, MD, PhD,<sup>46</sup> Myriam Gandia Martinez, MD, PhD,<sup>47</sup> David Díaz-Valle, MD, PhD,<sup>48</sup> Francisco J. López Longo, MD, PhD,<sup>49</sup> Joan M. Nolla, MD, PhD,<sup>50</sup> Enrique Raya Álvarez, MD, PhD,<sup>51</sup> Marcelino Revenga Martínez,

MD, PhD<sup>52</sup>, Julio José González-López, MD, PhD<sup>52</sup> Paz Rodríguez-Cundin, MD, PhD,<sup>1</sup> José L. Hernández, MD, PhD,<sup>1</sup> Miguel A. González-Gay, MD, PhD,<sup>1</sup> and Ricardo Blanco, MD, PhD,<sup>1</sup>.

<sup>1</sup>Rheumatology and Ophthalmology. Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, <sup>2</sup>Rheumatology. Hospital del Mar. Barcelona. Spain, <sup>3</sup>Rheumatology. Hospital de Valme, Sevilla. Spain, <sup>4</sup>Rheumatology and Ophthalmology. Hospital Clinic. Barcelona. Spain, <sup>5</sup>Ophthalmology. Hospital General Universitario de Valencia. Valencia. Spain, <sup>6</sup>Rheumatology and Ophthalmology. Hospital Peset. Valencia. Spain, <sup>7</sup>Rheumatology. Hospital Vall d'Hebron. Barcelona. Spain, <sup>8</sup>Ophthalmology. Hospital de León. Spain, <sup>9</sup>Ophthalmology. Hospital Universitario La Fe. Valencia. Spain, <sup>10</sup>Ophthalmology. Hospital San Cecilio. Granada. Spain, <sup>11</sup>Systemic Autoimmune Diseases Unit. Hospital San Cecilio. Granada. Spain, <sup>12</sup>Ophthalmology. Hospital Universitario IOBA. Valladolid. Spain, <sup>13</sup>Ophthalmology. Hospital de Cruces. Bilbao. Spain, <sup>14</sup>Rheumatology. Hospital de Toledo. Toledo. Spain, <sup>15</sup>Rheumatology and Ophthalmology. Hospital Universitario de Donostia. San Sebastián. Spain, <sup>16</sup>Rheumatology. Hospital Universitario de Basurto. Bilbao. Spain, <sup>17</sup>Rheumatology. Hospital Universitario de Móstoles. Madrid. Spain, <sup>18</sup>Rheumatology. Hospital General de Alicante. Alicante. Spain, <sup>19</sup>Rheumatology. Hospital La Paz. Madrid. Spain, <sup>20</sup>Rheumatology. Hospital Clínico San Carlos. Madrid. Spain, <sup>21</sup>Rheumatology. Hospital de Pontevedra. Pontevedra. Spain, <sup>22</sup>Ophthalmology. Hospital de Pontevedra. Pontevedra. Spain, <sup>23</sup>Rheumatology. Hospital Sierrallana. Torrelavega. Spain, <sup>24</sup>Rheumatology. Hospital Universitario de la Princesa, IIS-Princesa, Madrid. Spain, <sup>25</sup>Rheumatology. H. Reina Sofía. Córdoba. Spain, <sup>26</sup>Rheumatology. Hospital Clínico Universitario de Salamanca. Salamanca. Spain, <sup>27</sup>Rheumatology. C. Hospitalario Universitario A Coruña. A Coruña. Spain, <sup>28</sup>Rheumatology. Hospital Doctor Negrín. Las Palmas de Gran Canaria. Spain, <sup>29</sup>Rheumatology. Hospital Universitario Santiago de Compostela. A Coruña. Spain,

<sup>30</sup>Rheumatology. Hospital de Cabueñes. Gijón. Spain, <sup>31</sup>Rheumatology. Hospital Lucus Augusti. Lugo. Spain, <sup>32</sup>Rheumatology. Hospital San Pedro Alcántara. Cáceres. Spain, <sup>33</sup>Rheumatology. Hospital Virgen de la Arrixaca. Murcia. Spain, <sup>34</sup>Rheumatology. Jiménez Díaz Foundation University Hospital. Madrid. Spain, <sup>35</sup>Rheumatology. Instituto de Investigación Hospital 12 de octubre. Madrid. Spain, <sup>36</sup>Rheumatology. Hospital Universitario Fundación de Alcorcón. Madrid. Spain, <sup>37</sup>Ophthalmology. Hospital Clínico de Zaragoza. Zaragoza. Spain, <sup>38</sup>Rheumatology. Hospital de Mérida. Mérida. Spain, <sup>39</sup>Rheumatology. Germans Trias i Pujol Hospital. Barcelona. Spain, <sup>40</sup>Rheumatology. Hospital de Ferrol. A Coruña. Spain, <sup>41</sup>Ophthalmology and Rheumatology. Hospital Miguel Servet Zaragoza. Spain, <sup>42</sup>Rheumatology. Hospital Universitario Infanta Sofía. San Sebastián de los Reyes. Madrid. Spain, <sup>43</sup>Rheumatology. Hospital General Universitario de Elda. Alicante. Spain, <sup>44</sup>Rheumatology. Hospital Universitario Virgen del Rocío. Sevilla. Spain, <sup>45</sup>Rheumatology. Complejo Asistencial de Palencia. Palencia. Spain, <sup>46</sup>Rheumatology, Hospital Virgen de la Macarena. Sevilla. Spain, <sup>47</sup>Rheumatology. Hospital Puerta del Mar. Cádiz. Spain, <sup>48</sup>Ophthalmology. Hospital Clínico San Carlos. Madrid. Spain, <sup>49</sup>Rheumatology. Hospital de Móstoles. Madrid. Spain, <sup>50</sup>Rheumatology. Hospital Universitari de Bellvitge. Barcelona. Spain, <sup>51</sup>Rheumatology. Hospital Universitario San Cecilio. Granada, Spain. <sup>52</sup>Rheumatology and Ophthalmology. Hospital Universitario Ramón y Cajal. Madrid. Spain.

B. Atienza-Mateo, José L. Martín-Varillas and V. Calvo-Río shared first authorship.

J.L. Hernández, M.A. González-Gay and R. Blanco shared senior authorship.

**\*Joint corresponding authors-Address correspondence to:**

Miguel A. González-Gay or Ricardo Blanco, Rheumatology Division

Hospital Universitario Marqués de Valdecilla,

Avda. Valdecilla s/n., ES- 39008, Santander. SPAIN

Email addresses: [miguelaggay@hotmail.com](mailto:miguelaggay@hotmail.com), [rblanco@humv.es](mailto:rblanco@humv.es)

### **Competing interests**

Disclosures that might be interpreted as constituting of possible conflict(s) of interest for the study:

Dr. Belén Atienza-Mateo received grants/research supports from Roche, Celgene and GSK.

Dr. José Luis Martín-Varillas received grants/research supports from AbbVie, Pfizer and Celgene.

Dr. Vanesa Calvo-Río received grants/research supports from MSD and Roche, and had consultation fees/participation in company sponsored speaker's bureau from Abbott, Lilly, Celgene, Grünenthal and UCB Pharma.

Dr. Juan Sánchez-Burson received grants from Lilly and Janssen, and had fees/participation in company sponsored speaker's bureau from Pfizer.

Dr. Alfredo Adán received grants/research supports from AbbVie, and had consultation fees/participation in company sponsored speaker's bureau from AbbVie.

Dr. Elia Valls-Pascual received grants/research supports from Roche, Novartis and AbbVie, and had consultation fees/participation in company sponsored speaker's bureau from AbbVie, Lilly, Pfizer, MSD, Novartis, Janssen, Bristol Myers Squibb, UCB Pharma.

Dr. Agustí Sellas-Fernández received consultation fees/participation in company sponsored speaker's bureau from Abbott, Lilly, Celgene, Pfizer, Schering-Plough, Janssen, Novartis and Nordic Pharma.

Dr. Miguel Cordero-Coma was a lecturer for Abbvie, Merck Sharp & Dohme, Allergan and UCB. He also participated in Advisory Boards for Abbvie and Allergan, and had travel grants from Abbvie, UCB and Allergan.

Dr. Roberto Gallego received grants/research supports from Boehringer-Ingelheim, Novartis, Roche and Thrombogenics, and had consultation fees/participation in company sponsored speaker's bureau from Novartis, Roche, Bloss, Heidelberg Engineering, Indo and Novo Nordisk.

Dr. Norberto Ortego-Centeno received grants/research supports from Abbott.

Dr. José M. Herreras had consultation fees/participation in company sponsored speaker's bureau from AbbVie.

Dr. Ana Blanco had consultation fees/participation in company sponsored speaker's bureau from AbbVie.

Dr. Vega Jovaní received grants/research supports from AbbVie, MSD, Novartis and Pfizer, and had consultation fees/participation in company sponsored speaker's bureau from AbbVie.

Dr. Diana Peiteado López received grants/research supports from AbbVie, Lilly, MSD and Roche, and had participation in company sponsored speaker's bureau from AbbVie, Roche and MSD.

Dr. Esperanza Pato had consultation fees/participation in company sponsored speaker's bureau from AbbVie, MSD, Novartis and Nordic Pharma.

Dr. Miguel A. Caracuel-Ruiz received grants fees/participation in company sponsored speaker's bureau from Lilly, Sanofi-Genzyme and Amgen.

Dr. Antonio Atanes had consultation fees/participation in company sponsored speaker's bureau from Abbott, MSD, Menarini, Gebro, Grünenthal, Roche, Pfizer, Novartis, Celgene, Bristol Myers Squibb and Lacer.

Dr. Félix Francisco had consultation fees/participation in company sponsored speaker's bureau from Roche, Sanofi, Lilly, Abbott and Janssen.

Dr. Luis F. Linares Ferrando received grants/research supports from Pfizer, and had consultation fees/participation in company speaker's bureau from Abbvie, MSD, Novartis, Pfizer, Grunenthal and UCB.

Dr. Raquel Almodóvar González received grants/research supports and had consultation fees/participation in company speaker's bureau from Abbvie, Celgene, Gebro, Janssen, Lilly, MSD, Novartis, Pfizer and UCB.

Dr. Carmen Carrasco Cubero received grants/research supports and had consultation fees/participation in company speaker's bureau from Janssen, MSD, AbbVie, Novartis, Bristol Myers Squibb and Celgene.

Dr. Alejandro Olive had consultation fees from Lilly, Almirall, Abbie and Pfizer.

Dr. Cristina Fernández-Carballido received grants/research supports and had consultation fees/participation in company speaker's bureau from AbbVie, Celgene, Janssen, Novartis, Pfizer, MSD, Roche and UCB Pharma.

Dr. Esteban Rubio-Romero received grants/research supports from Lilly, Pfizer, Abbvie, Novartis, MSD, Celltrion, Sanofi, Roche, Gebro, Nordic, Grunenthal and UCB, and had consultation fees/participation in company sponsored speaker's bureau from Lilly, Sanofi, Biogen and Novartis.

Dr. Francisco J. López-Longo received grants/research supports from AbbVie and GSK, and had consultation fees/participation in company sponsored speaker's bureau from AbbVie, Actelion, Bristol Myers Squibb, GSK, MSD, Pfizer, Roche and UCB Pharma.

Dr. Joan M. Nolla received grants/research supports from Abbvie, Amgen, Biogen, BMS, Gebro, Lilly, MSD, Mylan, Roche, Sandoz, Sanofi and UCB, and had consultation fees/participation in company sponsored speaker's bureau from Abbvie, Amgen, BMS, Gebro, Kern, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi and UCB.

Dr. Enrique Raya Álvarez received grants/research supports from MSD, and had consultation fees/participation in company speaker's bureau from Lilly.

Dr. Julio José González-López received grants/research supports AbbVie and Bayer, and had consultation fees/participation in company sponsored speaker's bureau from Gilead.

Dr. Miguel A. González-Gay received grants/research supports from Abbott, MSD and Roche, and had consultation fees/participation in company sponsored speaker's bureau from Abbott, Pfizer, Roche and MSD.

Dr. Ricardo Blanco received grants/research supports from Abbott, MSD and Roche, and had consultation fees/participation in company sponsored speaker's bureau from Abbott, Pfizer, Roche, Bristol-Myers, Janssen and MSD.

No financial disclosure declared: Rosalía Demetrio-Pablo, Emma Beltrán, Marina Mesquida, María Victoria Hernández, Marisa Hernández-Garfella, Lucía Martínez-Costa, Manuel Díaz-Llopis, José L. García-Serrano, Alejandro Fonollosa, Ángel M. Garcia-Aparicio, Olga Maíz-Alonso, Ignacio Torre-Salaberri, Cruz Fernandez-Espartero, Juan Cruz, Carlos Fernández-Cid, Elena Aurrecoechea, Miriam García-Arias, Santos Castañeda, Carlos A. Montilla-Morales, Santos Insua, Senen González-Suárez, Amalia Sanchez-Andrade, Fernando Gamero, F. Romero-Bueno, A. Javier García-González, Enrique Minguez Muro, Águeda Prior, Julio Vázquez, Oscar Ruiz-Moreno, Fernando Jiménez-Zorzo, Javier Manero, Santiago Muñoz Fernandez, Fred Antón Pages, Francisco J. Toyos-Sáenz de Miera, Myriam Gandia Martinez, David Díaz-Valle, Marcelino Revenga Martínez, Paz Rodríguez-Cundin, José L. Hernández.

**Key indexing terms:** Uveitis, Behçet disease, infliximab, adalimumab, multicenter study

**ABSTRACT**

**Objective.** To compare the efficacy of infliximab (IFX) versus adalimumab (ADA) as first biologic drug in a large series of patients with refractory uveitis due to Behçet's disease (BD) for 1-year period.

**Methods.** Open-label multicenter study of IFX or ADA-treated patients with BD-uveitis refractory to conventional non-biologic treatment. IFX or ADA were chosen as first biologic treatment based on physician and patient agreement. Dosing schedule was: IFX: 3-5 mg/kg i.v. at 0, 2 and 6 weeks and every 4-8 weeks thereafter, and ADA: 40 mg/s.c./every other week without loading dose. Comparison between patients treated with IFX and patients treated with ADA was performed.

**Results.** 177 patients (316 affected eyes) were included. IFX was used in 103 and ADA in 74 cases. No significant differences at baseline were observed between IFX vs ADA groups regarding main demographic features, previous therapy and ocular severity. After one year of therapy, we observed an improvement in all ocular parameters in both groups. However, ADA therapy yielded better outcome in some parameters that in some cases yielded statistically significant differences: anterior chamber inflammation (78.18% in IFX-treated vs 92.31% in ADA-treated;  $p=0.06$ ), vitritis (78.95% vs 93.33%;  $p=0.04$ ), retinal vasculitis (97% vs 95%;  $p=0.28$ ), macular thickness ( $264.89\pm 59.74$  vs  $250.62\pm 36.85$ ;  $p=0.15$ ), best-corrected visual acuity ( $0.67\pm 0.34$  vs  $0.81\pm 0.26$ ;  $p=0.001$ ), and drug retention (84.95% vs 95.24%;  $p=0.042$ ).

**Conclusion.** Although IFX and ADA yields efficacy refractory BD uveitis, ADA appears to be associated with better outcome than IFX after one-year follow-up.

Behçet's disease (BD) is a systemic vasculitis characterized by recurrent oral and/or genital ulcers, skin lesions and ocular involvement, although it can affect multiple organs [1, 2]. One of the major causes of disability of BD is uveitis. Several studies indicate that the risk of severe visual loss ranges from 13% to 74% within 6 to 10 years after the onset of the uveitis [3-6].

The prognosis of ocular involvement has improved over the last decades due to the use of conventional and biologic immunosuppressive therapies [7]. According to the "Expert panel recommendations for the use of anti-TNF- $\alpha$  drugs in patients with ocular inflammatory disorders", published in 2014, anti-TNF therapy with infliximab (IFX) (good-quality evidence) or adalimumab (ADA) (moderate-quality evidence) may be considered as the first- or second-line corticosteroid-sparing therapy for patients with ophthalmic manifestations of BD, and IFX may be considered as the first- or second-line treatment for acute exacerbations of pre-existing BD [8].

In 2016, ADA was reported to be the only biologic drug that demonstrated efficacy in randomized double-blind Phase III studies in non-infectious intermediate, posterior uveitis and panuveitis [9-10]. Consequently, ADA was approved by the EMA and the FDA (<http://www.ema.europa.eu>) (<http://www.fda.gov>) in non-infectious non-anterior uveitis. However, underlying diseases included in the VISUAL trials were very heterogeneous. Furthermore, the VISUAL trials included very few cases of BD uveitis treated with ADA (12 patients [11%] in the VISUAL I and 10 patients [9%] in the VISUAL II). Therefore, conclusions on the efficacy of ADA in BD were scarce.

Moreover, little is known of differences in the outcome of BD uveitis treated with IFX or ADA. In this regard, there is only one single study comparing the efficacy of these two anti-TNF agents in adult patients with refractory non-infectious uveitis [11]. However, this study included a very heterogeneous group of patients, including unrelated entities to BD such as juvenile idiopathic arthritis, spondyloarthritis, or sarcoidosis. Moreover, patients with refractory uveitis due to BD only represented 36% of cases. Because of that, a specific comparison between IFX and ADA for refractory BD uveitis was absent.

Taking into account all these considerations, we aimed to compare the efficacy and safety of IFX versus ADA as the first biologic drug in a large series of patients with refractory uveitis exclusively due to BD for 1-year of follow-up.

## **PATIENTS AND METHODS**

### ***Design, Enrollment Criteria, and Definitions***

We set up an observational, open-label multicenter study including 177 patients with refractory uveitis due to BD who were treated with IFX or ADA as the first biologic therapy. Dosing schedule was the following: IFX: 3-5 mg/kg i.v. at 0, 2 and 6 weeks and every 4-8 weeks thereafter, and ADA: 40 mg/s.c./every other week (eow) without loading dose.

All of BD patients had uveitis refractory to glucocorticoids and had previously received at least one conventional synthetic immunosuppressive drug. IFX was used in 103 cases and ADA in 74. Partial information on 124 patients of this series was previously reported [12].

Patients were followed-up at 52 Uveitis Units of referral Spanish hospitals.

The diagnosis of BD was performed according to the proposed International Criteria for BD [13]. All of them fulfilled the recently proposed criteria for BD [14].

Since IFX is an off-label indication for uveitis, written informed consent was requested and obtained from all the patients. This was also requested for patients included in ADA group, since ADA was prescribed before the approval by the EMA and the FDA for the treatment of non-infectious and non-anterior uveitis.

Malignancy or systemic infectious diseases, including hepatitis B or C infection, were excluded before anti-TNF onset, as previously described [12,15-21].

To exclude latent tuberculosis, a tuberculin skin test (PPD) and/or an interferon- $\gamma$  assay (quantiFERON) and a chest radiograph were performed to all patients receiving biologic drugs, as indicated by the Spanish National Guidelines. If present, prophylaxis

with isoniazid was initiated at least 4 weeks before the onset of the biologic agent and maintained for 9 months.

Uveitis was anatomically classified according to the Standardization of Uveitis Nomenclature (SUN) Working Group [22].

Remission was defined as the absence of signs of any intraocular inflammation for at least 3 months. Intraocular inflammation was considered to be present if there was anterior or posterior chamber inflammation, retinal vasculitis, papillitis or cystoid macular edema (CME). A relapse was defined as a new flare of uveitis in a patient who was in remission [23].

The most frequent conventional immunosuppressive drugs and dosages given before ADA or IFX onset were cyclosporine A (CsA) (3-6 mg/kg/p.o./day), methotrexate (MTX) (7.5-25 mg/s.c./week), and azathioprine (AZA) (100-150 mg/p.o./day). In accordance with the VISUAL I and VISUAL II trials, the maintenance dose of ADA was 40 mg/s.c./eow. However, VISUAL I and II trials were published after the onset of the present study and, because of that, patients from our series did not receive a loading dose of ADA. Standard loading dose of IFX, 3-5 mg/kg/i.v., was given at 0, 2, and 6 weeks and then they received a maintenance dose every 4 to 8 weeks. Both anti-TNF agents were administered in combination with conventional immunosuppressive drugs in 78 patients with IFX (76.5%) and in 52 patients with ADA (70.3%) or as monotherapy in the remaining cases. The conventional drugs used in combination with ADA and IFX are shown in **Table 1**.

### **Outcome Variables**

The outcome variables were efficacy, safety and retention rate. To determine efficacy, the intraocular inflammation, macular thickness, visual acuity, the degree of immunosuppression load, the number of relapses and the sparing glucocorticoid effect were assessed. These outcome variables were recorded at baseline, 1 week, 2 weeks,

1 month, 3 months, 6 months and 1 year after IFX or ADA onset. They were assessed in each center according to a follow-up protocol agreed beforehand.

The degree of intraocular inflammation was evaluated according to the SUN Working Group [22]. Vitritis was assessed by the Nussenblatt scale [24]. The best-corrected visual acuity (BCVA) was estimated using the Snellen chart. Following SUN recommendations [22], improvement of anterior uveitis activity was defined as either a two-step decrease in the level of inflammation or a decrease to grade 0 in the level of inflammation (the scale is the following: 4, 3, 2, 1, 0.5 and 0). Inactive anterior uveitis (grade 0) was defined as <1 cell per field in the anterior chamber (AC) on slit lamp examination. A worsening activity was defined as either a two-step increases in the level of inflammation or an increase to grade 4. Similar definition was used for the improvement of vitritis haze.

Fluorescein angiography (FA) was performed to assess the presence of vasculitis. FA results were reviewed for the presence of vasculitis, papillitis and CME. Retinal vasculitis was defined as a retinal angiographic leakage, staining and/or occlusion on FA [4].

Choroiditis and retinitis were considered active or inactive depending on the presence or absence, respectively, of activity data on ophthalmoscopic examination and/or FA. High-Definition Optical Coherence Tomography (OCT) was the technique used to measure the macular thickness. It consists of a non-invasive imaging technique that uses light waves to obtain high-resolution cross-sectional images of the retina. Scans were obtained using the 512x128 scan pattern. Macular thickening was defined as a macular thickness >250  $\mu\text{m}$ , whereas CME was considered to be present if macular thickness was >300  $\mu\text{m}$ .

The degree of immunosuppression was calculated according to the semiquantitative scale proposed by Nussenblatt et al. [25, 26]. The grading scheme provides a combined, single numeric score for the total immunosuppression load per unit of body

weight per day. Grades for each agent (prednisone, CsA, AZA, MTX, and other immunosuppressants) ranged on a scale from 0 to 9, whereas mycophenolate mofetil ranged from 0 to 7. For patients receiving multiple medications, the sum of the grading score for each drug was used to calculate the total immunosuppression score at the baseline visit and at each visit on a scale from 0 to 15. Topical or periocular corticosteroid therapy was excluded from the calculation of the immunosuppressive load. The dose of biologic agents was not used to calculate the final immunosuppressive load.

### **Statistical Analysis**

Results were expressed as mean  $\pm$  standard deviation (SD) for variables with a normal distribution, or as median and interquartile range [25th-75th interquartile range (IQR)] for those not normally distributed. Continuous variables (normally and not normally distributed) were compared with the 2-tailed Student t test or the Mann Whitney U test, respectively. The chi-square test or the Fisher exact test was used for the dichotomous variables. The Wilcoxon signed-rank test was used to compare continuous variables between the two groups of treatment. The following variables were assessed and compared between baseline (first visit before anti-TNF $\alpha$  onset), 1 week, 2 weeks, 1 month, 3 months, 6 months and 1 year separately in each group: BCVA, AC cells, vitritis, retinal vasculitis, and OCT. Besides, mixed linear models are used with repeated measures data to accommodate the effects of treatment and time and the covariation between observations on the same subject at different times. This mixed model allows a greater flexibility in modeling covariance structures for repeated measures data, and adequately accounts for the within-subject time-dependent correlations. Further, the Bonferroni test for multiple comparisons was performed in order to control for the familywise error rate. Statistical significance was considered as a p-value < 0.05. Statistical analysis was performed by using the STATISTICA software (StatSoft, Tulsa, OK, USA).

## RESULTS

### ***Baseline demographic and clinical features in both ADA and IFX groups***

A total of 177 patients (316 affected eyes) with uveitis refractory to conventional immunosuppressive therapy were studied (**Table 1**). 103 patients (58%) were treated with IFX and 74 patients (42%) with ADA as the first biologic agent. In both groups, men slightly outnumbered women (55 men/48 women in the IFX group and 39 men/35 women in ADA group;  $p=0.93$ ). The mean age was similar in both groups ( $40.4\pm 10.1$  years in the IFX group and  $38.7\pm 11.3$  years in ADA group;  $p=0.29$ ). HLA-B51 was present in a similar proportion of patients in both groups (69.4% vs 68.9%;  $p=0.74$ ). In most cases uveitis was bilateral (79.61% in IFX group vs 77.03% in ADA group;  $p=0.68$ ).

Regarding previous therapy, there were not statistically significant differences in the administration of oral glucocorticoids between both groups (95% in IFX group vs 88% in ADA group;  $p=0.08$ ; mean maximum prednisone daily dosage  $54.35\pm 15.84$  mg/day in IFX group vs  $53.37\pm 17.52$  in ADA group;  $p=0.37$ ), intravenous pulses of 6-methylprednisolone (MP) (31% in both groups;  $p=0.98$ ). It was also the case for the percentage of patients treated with CsA, MTX, and cyclophosphamide (**Table 1**). However, we found a significantly higher percentage of patients receiving AZA before the onset of IFX (57%) compared with that of the ADA group (42%;  $p=0.049$ ). Also, no significant differences were observed in the dose of the different conventional immunosuppressive drugs in the IFX and ADA groups: CsA (mean dose:  $4.9\pm 0.8$  mg/kg/day vs  $4.8\pm 0.8$  mg/kg/day;  $p=0.88$ ), MTX (mean dose:  $15.6\pm 4.6$  mg/week vs  $16.7\pm 3.6$  mg/week;  $p=0.17$ ), and AZA (mean dose  $137.2\pm 32.3$  mg/day vs  $127.4\pm 25.3$  mg/day;  $p=0.14$ ). Moreover, the immunosuppression load score was similar in both groups (mean  $9.07\pm 4.14$  vs  $8.01\pm 5.24$ ;  $p=0.2$ ).

The median period between the onset of uveitis and the beginning of the anti-TNF therapy was also similar in both groups (median [IQR]; 36 months [12-72] vs 48 months [12-60];  $p=0.69$ ).

***Visual outcome, glucocorticoid-sparing effect and immunosuppression load score at one year of ADA and IFX therapy***

The standard loading dose of IFX (3-5 mg/kg i.v.) was given at 0, 2 and 6 weeks and then the patients received a maintenance dose every 4-8 week. The IFX onset regimen was as follows: 3 mg/kg i.v. and maintenance dose every 4 weeks (1 case), every 6 weeks (2 cases) and every 8 weeks (5 cases); 4 mg/kg i.v. and maintenance dose every 4 weeks (1 case); 5 mg/kg i.v. and maintenance dose every 4 weeks (15 cases), every 6 weeks (18 cases), every 7 weeks (1 case) and every 8 weeks (60 cases).

During the first year of treatment, we observed an improvement in all ocular parameters in both IFX and ADA groups. Nevertheless, improvement in some parameters yielded statistically significant differences in favor of ADA therapy: AC inflammation (78.18% with IFX vs 92.31% with ADA;  $p=0.06$ ), vitritis (78.95% with IFX vs 93.33% with ADA;  $p=0.04$ ), retinal vasculitis (97% with IFX vs 95% with ADA;  $p=0.28$ ), macular thickness ( $264.89\pm 59.74$  with IFX vs  $250.62\pm 36.85$  with ADA;  $p=0.15$ ) and BCVA ( $0.67\pm 0.34$  with IFX vs  $0.81\pm 0.26$  with ADA;  $p=0.001$ ).

Drug retention rate at one year was better with ADA (84.95% with IFX vs 95.24% with ADA;  $p= 0.042$ ).

More rapid improvement of AC cells and vitritis was found in the IFX group (data not shown). An explanation for that may be that ADA loading dose was not given in our series of patients. However, ADA group achieved better results at one-year therapy, with statistical significance in BCVA and retention rate.

In order to capture within patient correlation of repeated observations, we performed a mixed linear model using as covariates the factors that differ by a  $p$ -value on 0.1 in **Table 1**, as well as other plausible confounders. Once adjusted for the presence of

basal choroiditis, use of oral corticosteroids or azathioprine before anti-TNF onset, BCVA differences at 12 months, were still favorable to ADA vs IFX therapy ( $p=0.007$ ). The improvement in the values of BCVA in the different study periods is shown in **Figure 1**. Adding to the model the presence of vitritis, age, sex, or duration of uveitis before anti-TNF onset, did not change these results. However, once adjusted for these variables, there were no significant differences between both arms of therapy concerning vitritis, retinitis or OCT measurements.

At one year after the onset of anti-TNF therapy a reduction of the immunosuppression load score was also observed in both groups (from  $9.07\pm 4.14$  in the IFX group and  $8.01\pm 5.24$  in the ADA group [ $p=0.2$ ] at baseline to  $5.47\pm 3.19$  vs  $4.79\pm 3.52$  [ $p=0.38$ ], respectively at 1-year follow-up). The daily median dose of prednisone in both groups was reduced from 30 [20-45] mg (median [IQR]) at baseline to 5 [0-10] mg at 1 year in the IFX group, and from 20 [10-45] mg at baseline to 5 [2.5-10] mg at 1 year in the ADA group ( $p=0.9$ ).

#### ***Follow-up and side effects with ADA and IFX***

After a mean follow-up of  $31.52\pm 23.51$  and  $26.48\pm 18.57$  months with IFX and ADA respectively, ocular remission was achieved in 78 (76.47%) patients with IFX and in 65 (87.84%) patients with ADA ( $p=0.33$ ). However, the retention rate was statistically significant higher with ADA than with IFX (71.62% vs 44.12%;  $p < 0.001$ ). IFX was withdrawn in 57 (55.33%) and ADA in 21 (28.37%) cases ( $p < 0.01$ ). With respect to this, IFX was discontinued because of remission in 20 patients. In the remaining 37 patients the reasons for IFX discontinuation were inefficacy ( $n=18$ ), preference of another way of administration ( $n=9$ ), toxicity/side effects ( $n=8$ ), colon carcinoma ( $n=1$ ), and pregnancy desire ( $n=1$ ). In the case of ADA, it was discontinued because of remission in 6 patients whereas it was due to inefficacy ( $n=11$ ) or toxicity/side effects ( $n=4$ ) in the remaining 15 patients.

Drug withdrawal due to severe side-effects or toxicity was observed in 8 patients with IFX and 4 with ADA. The 8 cases with IFX were due to infusional reactions in 4 cases, and tuberculosis, *Mycobacterium avium* pneumonia, severe oral ulcers, and palmoplantar skin reaction one each respectively. Four patients discontinued ADA therapy because of lymphoma, bacterial pneumonia, severe local reaction at the injection site, and bacteremia by *Escherichia coli* respectively.

Data on remission, relapses, drug withdrawal and serious sides effects in both groups are shown in **Table 1**.

## DISCUSSION

In this multicenter study, we report on 177 cases of refractory BD-related uveitis treated with IFX (n=103) or ADA (n=74) as first biologic therapy. After one-year of follow up, patients treated with ADA achieved a better improvement of BCVA than those treated with IFX, as well as a greater retention rate, with a statistically significant difference between both groups. However, AC cells and vitritis improvement was observed more rapidly in the IFX group, what could be in part explained because of patients in ADA group did not receive the loading dose of 80 mg along with the next dose of 40 mg at one week as performed in the VISUAL trials since our study was carried out before these studies had been published.

Several studies have demonstrated the presence of high levels of TNF- $\alpha$  -a potent and central ubiquitous proinflammatory cytokine- in serum and aqueous humor of patients with uveitis, including cases with BD-related uveitis [27-29]. Anti-TNF- $\alpha$  agents, IFX -a human/mouse chimeric monoclonal IgG1 antibody specific for TNF- $\alpha$ , administered intravenously- and ADA -a fully human monoclonal IgG1 antibody also specific for TNF- $\alpha$ , administered subcutaneously- have demonstrated efficacy in the treatment of BD uveitis refractory to conventional immunosuppressive therapy [12, 26, 30-38].

In fact, ADA has recently been approved by the FDA and EMA for the use in non-infectious intermediate, posterior uveitis and panuveitis, included those due to BD. However, there are few studies comparing the efficacy of IFX and ADA to induce and maintain remission in these patients with refractory uveitis [11, 39, 40]. Moreover, these studies include generally patients with heterogeneous diseases, being patients with BD a minority of the total of the reported cases.

The present study compared the efficacy of IFX versus ADA as first biologic drug in a large series of patients with BD uveitis refractory to conventional immunosuppressive drugs. In this regard, before the onset of the biologic therapy, all patients had received systemic high-dose glucocorticoids and one or more conventional synthetic immunosuppressive drugs. However, despite this procedure, uveitis persisted active. Although our study showed a rapid and maintained improvement of all ocular parameters with both anti-TNF- $\alpha$  drugs, significant differences were observed regarding BCVA improvement mediated by ADA therapy. It is possible that ADA versus IFX differences had been even more evident if we would have performed an intention-to-treat study instead of performing a per-protocol analysis, because a higher percentage of patients discontinued IFX due to inefficacy.

Retention drug was also higher in the ADA group. This in part could be explained because of the route of administration since ADA is given subcutaneously in a rapid and comfortable way. Moreover, infusional reactions occur more frequently with IFX due to its chimeric nature and, probably, the occurrence of anti-drug antibodies may also be higher with IFX.

Minor adverse effects such as mild infusion reaction to IFX and local reactions at the site of the injection of ADA were the most commonly observed side effects. Severe complications leading to discontinuation of the biologic therapy were observed in 8 cases with IFX and 4 with ADA. These agents had to be withdrawn due to inefficacy in 18 cases in the IFX group and 11 with ADA, comprising a low percentage of cases (17.5% and 14.9%, respectively).

We realize that the study has several limitations due to its observational nature.

Because of that, further randomized, controlled trials comparing head to head both anti-TNF- $\alpha$  agents are required.

In conclusion, our study shows favorable results of ADA and IFX therapy at one year in BD-refractory uveitis, with a statistically significant difference in favor of ADA in the improvement of BCVA as well as in the retention rate.

## ACKNOWLEDGMENT

The authors acknowledge the members of the participating hospitals.

## REFERENCES

1. Kitaichi N, Miyazaki A, Iwata D, Ohno S, Stanford MR, Chams H. Ocular features of Behçet's disease: An international collaborative study. *Br J Ophthalmol*. 2007; 91:1579-82.
2. Yurdakul S, Yazici H: Behçet's syndrome. *Best Pract Res Clin Rheumatol*. 2008; 22:793-809.
3. Taylor SR, Singh J, Menezes V, Wakefield D, McCluskey P, Lightman S. Behçet's disease: visual prognosis and factors influencing the development of visual loss. *Am J Ophthalmol*. 2011; 152:1059-1066.
4. Tugal-Tutkun I, Onal S, Altan-Yaycioglu R, Huseyin Altunbas H, Urgancioglu M. Uveitis in Behçet disease: an analysis of 880 patients. *Am J Ophthalmol*. 2004;138:373-80.
5. Yang P, Fang W, Meng Q, Ren Y, Xing L, Kijlstra A. Clinical features of Chinese patients with Behçet's disease. *Ophthalmology* 2008;115:3128.
6. Ben-Ezra D, Cohen E. Treatment and visual prognosis in Behçet's disease. *Br J Ophthalmol*. 1986;70:589-592.
7. Schwartzman S. Advancements in the management of uveitis. *Best Pract Res Clin Rheumatol*. 2016; 30:304-15.
8. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. *Ophthalmology*. 2014;

- 121:785–96.
9. Jaffe GJ, Dick AD, Brézin AP, Nguyen QD, Thorne JE, Kestelyn P, et al. Adalimumab in Patients with Active Non-infectious Uveitis. *N Engl J Med*. 2016; 375: 932-43.
  10. Nguyen QD, Merrill PT, Jaffe GJ, Dick AD, Kurup SK, Sheppard J, et al. Adalimumab for prevention of uveitis flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. *Lancet*. 2016; 388: 1183-92.
  11. Vallet H, Seve P, Biard L, Baptiste Fraison J, Bielefeld P, Perard L, et al. Infliximab Versus Adalimumab in the Treatment of Refractory Inflammatory Uveitis: A Multicenter Study From the French Uveitis Network. *Arthritis Rheumatol*. 2016; 68:1522-30.
  12. Calvo-Río V, Blanco R, Beltran E, Sánchez-Bursón J, Mesquida M, Adán A, et al. Anti-TNF- therapy in patients with refractory uveitis due to Behcet's disease: a 1-year follow-up study of 124 patients. *Rheumatology (Oxford)*. 2014; 53: 2223-31.
  13. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *Lancet*. 1990; 335(8697):1078-80.
  14. Davatchi F, Assaad-Khalil S, Calamia KT, Crook JE, Sadeghi-Abdollahi B, Schirmer M, et al. The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatology Venereol*. 2014; 28:338-47.
  15. Calvo-Río V, de la Hera D, Beltrán-Catalán E, Blanco R, Hernandez M, Martínez-Costa L, et al. Tocilizumab in uveitis refractory to other biologic drugs: a study of 3 cases and a literature review. *Clin Exp Rheumatol*. 2014; 32(4 Suppl 84): S54-7.
  16. Calvo-Río V, Santos-Gómez M, Calvo I, González-Fernández MI, López-Montesinos B, Mesquida M, et al. Anti-Interleukin-6 Receptor Tocilizumab for Severe Juvenile Idiopathic Arthritis-Associated Uveitis Refractory to Anti-Tumor Necrosis Factor Therapy: A Multicenter Study of Twenty-Five Patients. *Arthritis Rheumatol*. 2017; 69:668-675.
  17. Santos-Gómez M, Calvo-Río V, Blanco R, Beltrán E, Mesquida M, Adán A, et al. The effect of biologic therapy different from infliximab or adalimumab in patients with refractory uveitis due to Behçet's disease: results of a multicentre open-label study. *Clin Exp Rheumatol* 2016; 34 (6 Suppl 102): S34-40.
  18. Riancho-Zarrabeitia L, Calvo-Río V, Blanco R, Mesquida M, Adan AM, Herreras JM, et al. Anti-TNF- $\alpha$  therapy in refractory uveitis associated with sarcoidosis: Multicenter study of 17 patients. *Semin Arthritis Rheum* 2015; 45:361-8.

19. Calvo-Río V, de la Hera D, Blanco R, Beltrán-Catalán E, Loricera J, Cañal J, et al. Golimumab in uveitis previously treated with other anti-TNF-alpha drugs: a retrospective study of three cases from a single centre and literature review. *Clin Exp Rheumatol*. 2014; 32:864-8.
20. Calvo-Río V, Blanco R, Santos-Gómez M, Rubio-Romero E, Cordero-Coma M, Gallego-Flores A, et al. Golimumab in refractory uveitis related to spondyloarthritis. Multicenter study of 15 patients. *Semin Arthritis Rheum*. 2016; 46:95-101.
21. Atienza-Mateo B, Calvo-Río V, Beltrán E, Martínez-Costa L, Valls-Pascual E, Hernández-Garfella M, et al. Anti-IL6-Receptor Tocilizumab in Refractory Uveitis Associated With Behçet's Disease. Multicenter Retrospective Study. *Rheumatology (Oxford)*. 2018 May 1; 57(5):856-864.
22. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol*. 2005; 140:509-16.
23. Bloch-Michel E., Nussenblatt RB: International Uveitis Study Group recommendations for the evaluation of intraocular inflammatory disease. *Am J Ophthalmol*. 1987; 103: 234-235.
24. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology* 1985; 92: 467-71.
25. Nussenblatt RB, Peterson JS, Foster CS, Rao NA, See RF, Letko E, et al. Initial evaluation of subcutaneous daclizumab treatments for noninfectious uveitis: a multicenter noncomparative interventional case series. *Ophthalmology* 2005; 112:764-70.
26. Díaz-Llopis M, Salom D, Garcia-de-Vicuña C, Cordero-Coma M, Ortega G, Ortego N, et al. Treatment of refractory uveitis with adalimumab: a prospective multicenter study of 131 patients. *Ophthalmology* 2012; 119:1575-81.
27. Santos Lacomba M, Marcos Martín C, Gallardo Galera JM, Gómez Vidal MA, Collantes Estévez E, Ramírez Chamond R, et al. Aqueous humor and serum tumor necrosis factor alpha in clinical uveitis. *Ophthalmic Res* 2001; 33:251-5.
28. Pérez-Guijo V, Santos-Lacomba M, Sanchez-Hernandez M, Castro-Villegas M del C, Gallardo-Galera JM, Collantes-Estevez E. Tumour necrosis factor-alpha levels in aqueous humour and serum from patients with uveitis: the involvement of HLA-B27. *Curr Med Res Opin* 2004; 20:155-7.

29. Nakamura S, Sugita M, Tanaka T, Ohno S. Enhanced production of in vitro tumor necrosis factor- $\alpha$  from monocytes in Behçet's disease. *Nihon Ganka Gakkai Zasshi* 1992; 96:1282-85.
30. Okada AA, Goto H, Ohno S, Mochizuki M. Ocular Behçet's Disease Research Group of Japan. Multicenter study of infliximab for refractory uveoretinitis in Behçet disease. *Arch Ophthalmol* 2012; 130:592-8.
31. Sugita S, Yamada Y, Mochizuki M. Relationship between serum infliximab levels and acute uveitis attacks in patients with Behçet disease. *Br J Ophthalmol* 2011; 95:549-52.
32. Keino H, Okada AA, Watanabe T, Taki W. Decreased ocular inflammatory attacks and background retinal and disc vascular leakage in patients with Behçet's disease on infliximab therapy. *Br J Ophthalmol* 2011; 95:1245-50.
33. Tugal-Tutkun I, Mudun A, Urgancioglu M, Kamali S, Kasapoglu E, Inanc M, et al. Efficacy of infliximab in the treatment of uveitis that is resistant to treatment with the combination of azathioprine, cyclosporine, and corticosteroids in Behçet's disease: an open-label trial. *Arthritis Rheum* 2005; 52:2478-84.
34. Niccoli L, Nannini C, Benucci M, Chindamo D, Cassarà E, Salvarani C, et al. Long-term efficacy of infliximab in refractory posterior uveitis of Behçet's disease: a 24-month follow-up study. *Rheumatology (Oxford)* 2007; 46:1161-64.
35. Bawazeer A, Raffa LH, Nizamuddin SH. Clinical experience with adalimumab in the treatment of ocular Behçet disease. *Ocul Immunol Inflamm* 2010; 18:226-32.
36. Takase K, Ohno S, Ideguchi H, Uchio E, Takeno M, Ishigatsubo Y. Successful switching to adalimumab in an infliximab-allergic patient with severe Behçet disease-related uveitis. *Rheumatol Int* 2011; 31:243-5.
37. Perra D, Alba MA, Callejas JL, Mesquida M, Ríos-Fernández R, Adán A, et al. Adalimumab for the treatment of Behçet's disease: experience in 19 patients. *Rheumatology (Oxford)* 2012; 51:1825-31.
38. Calvo Catalá J, Campos Fernández C, Rueda Cid A, González-Cruz Cervellera MI, Baixauli Rubio A, Pastor Cubillo MD. Efficacy of adalimumab in Behçet's disease. Description of 6 cases. *Reumatol Clin* 2011; 7: 258-261.
39. Zannin ME, Birolo C, Gerloni VM, Misericocchi E, Pontikaki I, Paroli MP, et al. Safety and efficacy of infliximab and adalimumab for refractory uveitis in juvenile idiopathic arthritis: 1-year follow-up data from the Italian Registry. *J Rheumatol*. 2013; 40:74-9.
40. Simonini G, Taddio A, Cattalini M, Caputo R, De Libero C, Naviglio S, et al. Prevention of flare recurrences in childhood-refractory chronic uveitis: An open-

label comparative study of adalimumab versus infliximab. *Arthritis Care Res.* 2011;63: 612-618.

## FIGURE LEGENDS

**FIGURE 1.** Adjusted best corrected visual acuity (BCVA) (media  $\pm$  SD) in both treatment's arms.

**TABLE 1.** Main baseline features and follow-up of a series of 177 patients with refractory uveitis due to Behçet's disease undergoing infliximab (IFX) or adalimumab (ADA) therapy.

	IFX group (N=103)	ADA group (N=74)	p
<b>Number of patients/affected eyes, (n/n)</b>	103/185	74/131	
<b>Age, mean (SD) years</b>	40.4 (10.1)	38.7 (11.3)	0.29
<b>Sex, men/women, n/n</b>	55/48	39/35	0.92
<b>HLA-B51 positive, (%)</b>	69.4	68.9	0.74
<b>Duration of uveitis before anti-TNF<math>\alpha</math>, median [IQR] months</b>	36 [12-72]	24 [12-60]	0.69
<b>Ocular features at the time of anti TNF-<math>\alpha</math> onset</b>			
AC cells, median [IQR]	1 [0-2]	1 [0-2]	0.25
Vitritis, median [IQR]	1 [0-2]	1 [0-2]	0.12
BCVA, mean (SD)	0.50 (0.35)	0.56 (0.34)	0.08
Macular thickness, mean (SD)	331.11 (131.97)	346.37 (136.14)	0.49
Presence of retinal vasculitis, n	114	78	0.51
Presence of choroiditis, n	41	10	<b>&lt;0.01</b>
<b>Pattern of uveitis, (n/%)</b>			
Bilateral	82 (79.61)	57 (77.03)	0.68
Unilateral	21 (20.39)	17 (22.97)	0.68
Anterior	11 (10.68)	14 (18.92)	0.19
Posterior	28 (27.18)	14 (18.92)	0.19
Panuveitis	64 (62.14)	45 (60.81)	0.19
Intermediate	0 (0)	1 (1.35)	0.19
<b>Treatment before anti TNF-<math>\alpha</math> onset, (%)</b>			
Oral corticosteroids	95	88	0.08
Intravenous pulses of MP	31	31	0.98
CsA	75	78	0.65
AZA	57	42	<b>0.049</b>
MTX	44	42	0.77
Other treatments	3.84	1.92	0.41
<b>Prednisone dose at anti TNF-<math>\alpha</math> onset, mean (SD), mg/d</b>	54.35 (15.84)	53.37 (17.52)	0.37
<b>Combined treatment, (%)</b>			
AZA	<b>76.5</b>	<b>70.3</b>	<b>0.35</b>
CsA	21.8	19.2	
MTX	41.1	55.7	
CFM	33.3	21.1	
CFM	1.3	0.0	
MMF	1.3	3.8	
FK-506	1.3	0.0	
<b>Follow-up on anti TNF<math>\alpha</math> therapy, mean (SD), months</b>			
Remission, n (%)	31.52 (23.51)	26.48 (18.57)	0.13
Relapses, mean (SD)	78 (76.47)	61 (82.43)	0.34
Drug withdrawal, n (%)	1.13 (2.62)	1.66 (8.62)	0.61
Remission, n (%)	57 (55.33)	21 (28.37)	<b>&lt;0.01</b>
Inefficacy, n (%)	20 (19.41)	6 (8.45)	0.58
Severe side-effects/toxicity, n (%)	18 (17.47)	11 (14.86)	0.09
Others, n (%)	8 (7.76)	4 (3.88)	0.58
Others, n (%)	11 (10.68)	0 (0)	<b>0.03</b>
Serious side-effects, n (per 100 patients/year)	4 (1.48)	4 (2.46)	0.40

**Abbreviations:** ADA, adalimumab; AZA, azathioprine; CFM, cyclophosphamide; CsA, cyclosporine A; FK-506, tacrolimus; IFX, infliximab; IQR: interquartile range; MMF, mycophenolate mofetil; MTX, methotrexate; MP, methylprednisolone; SD: standard deviation; TNF- $\alpha$ : tumor necrosis factor alpha.

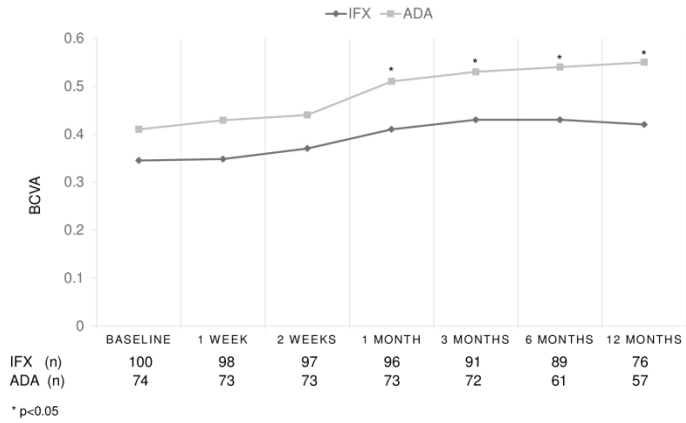


FIGURE 1. Adjusted best corrected visual acuity (BCVA) (media ± SD) in both treatment's arms.

338x190mm (200 x 200 DPI)

**TABLE 1.** Main baseline features and follow-up of a series of 177 patients with refractory uveitis due to Behçet's disease undergoing infliximab (IFX) or adalimumab (ADA) therapy.

	IFX group (N=103)	ADA group (N=74)	p
<b>Number of patients/affected eyes, (n/n)</b>	103/185	74/131	
<b>Age, mean (SD) years</b>	40.4 (10.1)	38.7 (11.3)	0.29
<b>Sex, men/women, n/n</b>	55/48	39/35	0.92
<b>HLA-B51 positive, (%)</b>	69.4	68.9	0.74
<b>Duration of uveitis before anti-TNF<math>\alpha</math>, median [IQR] months</b>	36 [12-72]	24 [12-60]	0.69
<b>Ocular features at the time of anti TNF-<math>\alpha</math> onset</b>			
AC cells, median [IQR]	1 [0-2]	1 [0-2]	0.25
Vitritis, median [IQR]	1 [0-2]	1 [0-2]	0.12
BCVA, mean (SD)	0.50 (0.35)	0.56 (0.34)	0.08
Macular thickness, mean (SD)	331.11 (131.97)	346.37 (136.14)	0.49
Presence of retinal vasculitis, n	114	78	0.51
Presence of choroiditis, n	41	10	<b>&lt;0.01</b>
<b>Pattern of uveitis, (n/%)</b>			
Bilateral	82 (79.61)	57 (77.03)	0.68
Unilateral	21 (20.39)	17 (22.97)	0.68
Anterior	11 (10.68)	14 (18.92)	0.19
Posterior	28 (27.18)	14 (18.92)	0.19
Panuveitis	64 (62.14)	45 (60.81)	0.19
Intermediate	0 (0)	1 (1.35)	0.19
<b>Treatment before anti TNF-<math>\alpha</math> onset, (%)</b>			
Oral corticosteroids	95	88	0.08
Intravenous pulses of MP	31	31	0.98
CsA	75	78	0.65
AZA	57	42	<b>0.049</b>
MTX	44	42	0.77
Other treatments	3.84	1.92	0.41
<b>Prednisone dose at anti TNF-<math>\alpha</math> onset, mean (SD), mg/d</b>	54.35 (15.84)	53.37 (17.52)	0.37
<b>Combined treatment, (%)</b>			
<b>AZA</b>	<b>76.5</b>	<b>70.3</b>	<b>0.35</b>
AZA	21.8	19.2	
CsA	41.1	55.7	
MTX	33.3	21.1	
CFM	1.3	0.0	
MMF	1.3	3.8	
FK-506	1.3	0.0	
<b>Follow-up on anti TNF<math>\alpha</math> therapy, mean (SD), months</b>			
Remission, n (%)	31.52 (23.51)	26.48 (18.57)	0.13
Relapses, mean (SD)	78 (76.47)	61 (82.43)	0.34
Drug withdrawal, n (%)	1.13 (2.62)	1.66 (8.62)	0.61
Remission, n (%)	57 (55.33)	21 (28.37)	<b>&lt;0.01</b>
Inefficacy, n (%)	20 (19.41)	6 (8.45)	0.58
Severe side-effects/toxicity, n (%)	18 (17.47)	11 (14.86)	0.09
Others, n (%)	8 (7.76)	4 (3.88)	0.58
Others, n (%)	11 (10.68)	0 (0)	<b>0.03</b>
Serious side-effects, n (per 100 patients/year)	4 (1.48)	4 (2.46)	0.40

**Abbreviations:** ADA, adalimumab; AZA, azathioprine; CFM, cyclophosphamide; CsA, cyclosporine A; FK-506, tacrolimus; IFX, infliximab; IQR: interquartile range; MMF, mycophenolate mofetil; MTX, methotrexate; MP, methylprednisolone; SD: standard deviation; TNF- $\alpha$ : tumor necrosis factor alpha.