USE OF TOCILIZUMAB IN AORTITIS. A MULTICENTER STUDY OF 79 PATIENTS


Rheumatology, Internal Medicine and Pathology Units, Santander, Navarra, Madrid, Tomelavega, Leon, Pontevedra, Barcelona, Móstoles, Madrid, Santiago de Compostela, Vigo, Alicante, Lugo, Badalona, Palencia, Alcázar de San Juan, A Coruña, Granada, Bilbao, Avilés, Castelón, Salamanca, Zaragoza, Valencia, Menorca, Málaga, Ávila, Gijón, Ourense, Tenerife, Sevilla, Lérida, Spain

Background: Aortitis can be idiopathic or associated with other conditions. It is frequently refractory to conventional immunosuppressive therapy. Tocilizumab (TCZ), anti-IL-6 receptor antibody seems to be effective and safe.

Objectives: Our aim was to assess the efficacy and safety of TCZ at short and long follow-up in a series of patients with Aortitis.

Methods: Retrospective, multicenter study of 79 patients diagnosed of inflammatory aortitis based on imaging techniques (PET/CT, CT angiography and/or MR angiography).

Results: We study 79 patients (61 w/ 18 m), 59 (74.7%) cases were secondary to Giant Cell Arteritis (GCA), while 20 (25.3%) were idiopathic. The mean age was 71±8.5 years vs 64±7.1 years, respectively (p=0.001). At time of disease diagnosis more than a half of patients (59.5%) presented as main symptom polymyalgia rheumatica (PMR). Aortitis was diagnosed with PET/CT (71 patients), angioRMN (12 patients) and angioRNA (8 patients). Prior to TCZ treatment, 61 (77.2%) patients had received conventional immunosuppressive drugs, 53 (76.7%) of them received MTX. After 24 months of treatment with TCZ, more than 75% of patients reached a prolonged remission in both groups (p=0.527), with only 4% of relapses after the same follow-up period (p=1.000). 40 (50.6%) patients had a control image technique (PET/CT) throughout follow up. 4 (3 secondary to GCA and 1 idiopathic) patients reached a complete improvement in uptake after one year of treatment. Conclusion: Our results show that idiopathic aortitis occurs in younger patients compared with aortitis secondary to GCA. TCZ proved to be effective in both pathologies, allowing clinical and analytical improvement, as well as a reduction of corticoid dose, without increasing the risk of relapse. However, the improvement in imaging techniques seems to be slower.

REFERENCE

Disclosure of Interests: Monica Calderón-Góorce: None declared, J. Loricer: None declared, D. Prieto-Peria: None declared, Vicente Aldeasoro: None declared, Santos Cañasiedo: Ignacio Vílitez-Blanco: None declared, Clara Moriana: None declared, Susana Romero-Yuste: None declared, J. Narváez: None declared. Bristol-Myers Squibb: Catalina Gomez-Arango: None declared, Eva Perez-Pampin: None declared, Rafael Melero: None declared, Marcelino Revenga: None declared, Noelia Alvarez-Rivas: None declared, Francisca Siviera: None declared, Maria Alvarez del Buero: None declared, Luisa Marena Rojas: None declared, Eva Galindez: None declared, Beatriz Arca: None declared, Roser Solans-Laquè: None declared, Carlos Vázquez: None declared, Eva Salgado-Pérez: None declared, Francisco J. Toyos: None declared, Nagore Fernandez-Llano: None declared, Antonia Garcia: None declared, Carmen Larena: None declared, Natalia Pons-fontana: None declared, Vesna Calvo-Rio: None declared, Carmen González-Vela: None declared, Alfonso Corrales: None declared, Maria Varela-Garcia: None declared, Elena Aurrecoechea: None declared, Raquel Dos-Santos: None declared. José Luis Martin-Varillas: None declared, Miguel A. Gonzalez-Gay: Grant/research support from Abbvie, Pfizer, Roche and Sanofi., Ricardo Blanco: Grant/research support from Abbvie, MSD, Roche, Consultant for: Abbvie, Pfizer, Roche, Bristol-Myers, Janssen. Speakers bureau: Abbvie, Pfizer, Roche, Bristol-Myers, Janssen.


OFF-LABEL USE OF BIOLOGICAL THERAPIES IN RELAPSING AND/OR REFRACTORY POLYARTERITIS NODOSA

Alice Canzian1, Omer Karadag2, Anne Contis3, Francois Maurier, Silvia Sartorelli4, Laure Denis5, Sebastien Sanges6, Claire De Moreuil7, Cécile-Audrey Durell8, Stephanie Dunput9, Marie Jache10, Diane Rouzaud11, Carlo Salvarani12, Franco Schiavin13, Lorenzo Dagna13, Fabrio Bonnet13, David Jacob13, Loic Guilly14, Benjamin Terrier15, University of Padova, Padova, Italy; 2Hacettepe University, Ankara, Turkey; 3CHU de Bordeaux, bordeaux, France; 4Private Metz Hospital, Metz, France; 5IRCCS San Raffaele Hospital, Milan, Italy; 6CHU de Clermont-Ferrand, Clermont-Ferrand, France; 7CHU de Lille, Lille, France; 8CHU de Brest, Brest, France; 9CHU de Lyon, Lyon, France; 10Paris, France; 11Université de Modena e Reggio Emilia, Reggio Emilia, Italy; 12University of Padova, Padova, Italy; 13University of Cambridge, Cambridge, United Kingdom; 14Université Paris Descartes, Paris, France; 15Paris Descartes University, Paris, France

Background: Polyarteritis nodosa (PAN) is a rare systemic necrotizing vasculitis of medium- and small-sized arteries, not associated with antineutrophil cytoplasmic antibodies (ANCA). Conventional treatments include glucocorticoids (GCs) for non-severe disease and a combination of GCs and immunosuppressive agents for severe disease. Nevertheless, some patients have refractory and/or relapsing disease.

Objectives: We examined the use of off-label biological therapy for relapsing/refractory PAN.

Methods: This retrospective European collaborative study included patients with PAN meeting ACR criteria and/or Chapel Hill Consensus Conference 2012 definitions. Treatment efficacy and safety were recorded. Remission was defined as the absence of vasculitis manifestations (BVAS = 0) with a prednisone dose ≤5 mg/day. Partial response was defined as a BVAS = 0 with a prednisone dose between 6 and 10 mg/day.

Results: Fifty-one patients (24 men, 27 women; median age 51 years) were included. Eighteen (35%) patients received TNF-alpha blockers, 16 (31%) received rituximab, 16 (31%) received mycophenolate mofetil (47%). At inclusion, median BVAS was 5 (range 0-18), including 5 (2-12) in the TNF-alpha blockers group, 5 (2-12) in the RTX group and 4 (0-6) in the TCZ group. After median follow-up of 34.4 months (IQR 21.5-59.5), remissions, partial responses and treatment failure, respectively, were noted in 41%, 6% and 53% for TNF-alpha blockers recipients, 25%, 12% and 63% for RTX recipients, and 25%, 0% and 43% for TCZ recipients. No remission was noted in patients treated with anakinra, alemtuzumab and abatacept. Median BVAS dropped to 3 at 6 months, 0 at 12 months and 0 at last follow-up in the TNF-alpha blockers group, to 3.5, 0 and 2 in the RTX group, respectively, and 0, 0 and 0 in the TCZ group. A GC-sparing effect seemed more important with TNF-alpha blockers and TCZ. Median GCs dose decreased from the baseline 15 mg/day to 10 at 6 months, 5 at 12 months and 5 at last follow-up in the TNF-alpha blockers group, from 15 mg/day to 10 at 6 months, 5 at 12 months and 5 at last follow-up in the RTX group, and from 15 mg/day to 7 at 6 months, 5 at 12 months and 5 at last follow-up in the TCZ group.

Four (22%) patients stopped TNF-alpha blockers because of allergic reaction in one and refractory disease in 3. Six (38%) stopped RTX because of refractory disease. Finally, 4 (44%) stopped TCZ because of adverse

Disclosure of Interests: 1Alice Canzian: None declared, Omer Karadag: None declared, Anne Contis: None declared, Francois Maurier: None declared, Silvia Sartorelli: None declared, Laure Denis: None declared, Sebastien Sanges: None declared, Claire De Moreuil: None declared, Cécile-Audrey Durell: None declared, Stephanie Dunput: None declared, Marie Jache: None declared, Diane Rouzaud: None declared, Carlo Salvarani: None declared, Franco Schiavin: None declared, Lorenzo Dagna: None declared, Fabrio Bonnet: None declared, David Jacob: None declared, Loic Guilly: None declared, Benjamin Terrier: None declared, University of Padova, Padova, Italy; 2Hacettepe University, Ankara, Turkey; 3CHU de Bordeaux, bordeaux, France; 4Private Metz Hospital, Metz, France; 5IRCCS San Raffaele Hospital, Milan, Italy; 6CHU de Clermont-Ferrand, Clermont-Ferrand, France; 7CHU de Lille, Lille, France; 8CHU de Brest, Brest, France; 9CHU de Lyon, Lyon, France; 10Paris, France; 11Université de Modena e Reggio Emilia, Reggio Emilia, Italy; 12University of Padova, Padova, Italy; 13University of Cambridge, Cambridge, United Kingdom; 14Université Paris Descartes, Paris, France; 15Paris Descartes University, Paris, France

References
COOPERATION OF T FOLLICULAR HELPER CELLS AND B CELLS IN TERTIARY LYMPHOID STRUCTURES IN TAKAYASU ARTERITIS

Anne-Claire Desbois1, Anna Maciejewski-Duval1, Paul Régnier1,2, Marie Jachiet1, Diane Rouzaud1, Carlo Salvarani1, Daniela Saggese1,2, Paul Régnier1,2, Guillaume Darrasse-Jèze2, Patrice Cacoub2, David Klatzmann2, Fabien Koskas2, Marie Karadag3,4,5,6, Benjamin Terrier2, Guillaume Darrasse-Jèze2, Patrice Cacoub2, David Klatzmann2, Fabien Koskas2.

1GHPS, Paris, France
2Groupe Hospitalier La Pitié Salpêtrière, Paris, France
3HEPG, Paris, France
4Institut de Récherche en Transplantation et Santé, Lyon, France
5Division of Rheumatology, Istanbul University – Cerrahpaşa Medical Faculty, Department of Ophthalmology, Istanbul, Turkey
6Istanbul University – Cerrahpasa Medical Faculty, Department of Internal Medicine, Division of Rheumatology, Istanbul, Turkey

Background: Takayasu’s arteritis (TA) and giant cell arteritis (GCA), the two most common types of large vessel vasculitides (LVV), are characterized by an arterial inflammatory granulomatous infiltrate mainly located in the media and the adventitia. However, distinct histological features of the immune response are poorly known.

Objectives: To investigate distinct pathological mechanisms of the immune response in patients with GCA and TA.

Methods: We performed comparative immunohistochemistry analysis of aorta of GCA and TA patients. We performed microarray gene analysis of purified CD4+ T cells of TA and GCA patients. Reverse transcriptase PCR, flow cytomtery analysis and cell culture were used to investigate T and B cells subpopulations in 54 patients with TA, 52 with GCA and 60 controls.

Results: We found higher proportion of tertiary lymphoid structures composed of CXCR5+, CD4+, PD-1+ and CD20+ cells in inflammatory aortic lesions in TA compared to GCA. We demonstrated increased proportion of aortic B cells in TA.

We next evaluated differentiation of circulating CD4+ T cells in both diseased groups. CD4+CXCR5- and CD4+CXCR5+ cells of TA compared to GCA patients, we identified a specific “T follicular helper” (Th) signature in TA patients. We also found a specific Th17 signature in TA patients. Flow cytometry analysis confirmed increased circulating Th1, defined as CXCR5+ CD4+ T cells compared to GCA and healthy donors (HD) [median of 15.4 (10.0;23.8) versus 5.3 (1.4; 12.2%); p<0.001] in TA, GCA and HD, respectively. Among Th17 subpopulations, Th17, CXCR5+CCR6+CXCR3-CD4+ cells were specifically increased in TA. Functionally, CXCR5+CD4+ T cells of TA patients helped B cells to differentiate into memory cells, to proliferate and to secrete type I immunoglobulins.

We sequenced the TCR repertoire u/j in CD3+CD4+CXCR5+ and CD3+CD4+CXCR5+ cells, in aortic and blood samples from 2 patients. In both patients, we identified oligoimolecular profile of TCR repertoire only for aortic CXCR5+ cells, suggesting antigenic selection of CXCR5+ CD4+ T cells.

Conclusion: We provide evidence of the presence of tertiary lymphoid structures composed of Th and B cells in TA aorta. We identified a specific Th17 signature in circulating CD4+ T cells that distinguishes TA and GCA patients. The key cooperation of Th1 and B cells in TA and the oligoclonal repertoire of CXCR5+ CD4+ T cells strongly suggest the role of antigenic trick.

Disclosure of Interests: : Anne-Claire DESBOIS Speaker bureau: SOBI on 2015, Anna Maciejewski-Duval: None declared, Paul Régnier: None declared, Valentin QUINIOU: None declared, Cloé Comarmond: None declared, Hélène Vallet: None declared, Patrick Bruneval: None declared, Fabien Koskas: None declared, Marlène Garido: None declared, Guillaume Darrasse-Jèze: None declared, Patrice cabouc Consultant for: d’Abbivie, Astra Zeneca, Bayer, Boehringer Ingleheim, Gilead, Glaxo Smith Kline, Janssen, Merck Sharp Dohme, Pfizer, Roche, Servier, and Vifor., Speakers bureau: d’Abbivie, Astra Zeneca, Bayer, Boehringer Ingleheim, Gilead, Glaxo Smith Kline, Janssen, Merck Sharp Dohme, Pfizer, Roche, Servier, and Vifor., David Saadoun Grant/ research support from: Roche, Abbvie, Consultant for: Janssen, Celgene, Abbvie, Roche


FACTORS ASSOCIATED WITH DAMAGE PROGRESSION IN BEHÇET’S SYNDROME UVEITIS

Yilmaz Ozyazgan1, Didar Ucar1, Mustafa Erdogar2, Yezin Ozgüzer3, Gülen Hatemi4, Sebahatn Yurdakul5, Vedat Hamuryudan6, Izzet Fresko2, Melike Melioglou7, Emine Seyahi8, Serdal Ugurlu9, Hasan Yazıcı10, Istanbul University – Cerrahpaşa Medical Faculty, Department of Ophthalmology, Istanbul, Turkey

Background: Uveitis in Behçet’s syndrome (BS) follows a recurrent disease course with inflammatory exacerbations causing damage in the uvea, retina and optic nerve even with treatment. Frequent attacks and posterior involvement are considered as predictors of poor visual outcome.

Objectives: The aim of this study is to delineate the predictors of damage in more detail using a standard screening method among a group of BS patients with long-term follow-up.

Methods: Patients with uveitis who were registered in our multidisciplinary BS clinic between 1990 and 2008 were screened. Among these, 50 patients who were followed for at least 10 years, who were regularly seen in our clinic at least once in every 4 months, who did not have > Grade 2 damage at baseline, and who represented different levels of damage severity during the last visit (between Grade 0 and 5) were selected. The damage severity was graded according to a validated damage grading instrument (5=worst) specifically developed for BS uveitis (Ozyazgan et al. in preparation). One patient was later excluded because it was realized that he did not fulfill these criteria. A standard form was used for retrieving data on demographics, baseline and final visual acuities, number and localization (anterior/posterior/panuveitis) of attacks during follow-up, presence of retinal infiltration, retinal hemorrhage and hypopyon uveitis. Candidate factors for damage progression were compared between patients who had a progression in damage score and those who did not.

Results: 98 eyes of 49 patients (M:F=35:14, mean age at baseline 27±8 years, mean follow-up duration 20±5.5 years, mean number of visits 76.5±35.2) were evaluated. The mean visual acuity was 0.02±0.08 at baseline and 0.47±0.52 at the final visit. The median number of attacks was 13±2.94. Damage grades at baseline were Grade 0 in 79, Grade 1 in 16 and Grade 2 in 3 eyes. Damage grades at final visit were Grade 0 in 15, Grade 1 in 21, Grade 2 in 32, Grade 3 in 12, Grade 4 in 10 and Grade 5 in 8 eyes. There was damage progression in 81/98 eyes at the final visit. Isolated anterior uveitis attacks were not associated with progression of damage (2.5±2.9 vs 2.8±5.5, p=0.70). Parameters that were significantly more frequent among patients with damage progression were: number of attacks (14.5±10.8 vs 23.3±12.3; p<0.008), number of posterior attacks (0.41±0.2 vs 6.5±4.9, p<0.001), number of panuveitis attacks (0.8±1.3 vs 6.6±5.0, p<0.001), number of attacks with severe vitrous opacity preventing examination of the retina (0 vs 3.2±3.8, p<0.001), retinal infiltration (0.2±0.4 vs 1.4±1.9, p<0.001) and retinal hemorrhages in the arcuate region (0.1±0.2 vs 0.7±1.4, p<0.001), and the number of hypopyon attacks (0.2±1.0 vs 0.9±1.3, p=0.019).

Conclusion: This study confirmed that the anterior uveitis attacks are not associated with progressive damage in BS, whereas posterior and panuveitis attacks, attacks causing severe vitreous opacity, retinal infiltrates and hemorrhage in the arcuate region and hypopyon attacks are important predictors of damage. Patients showing these features should be treated more aggressively.

REFERENCE