

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

**"How I treat" autoimmune diseases: State of the art on the management of rare rheumatic diseases and ANCA-associated systemic idiopathic vasculitis**

**This is the author's manuscript**

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/1647996> since 2019-02-11T16:22:30Z

*Published version:*

DOI:10.1016/j.autrev.2017.07.015

*Terms of use:*

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

**This is the author's final version of the contribution published as:**

Roccatello D.

"How I treat" autoimmune diseases: State of the art on the management of rare rheumatic diseases and ANCA-associated systemic idiopathic vasculitis. *Autoimmun Rev.* 2017 Oct;16(10):995-998. doi: 10.1016/j.autrev.2017.07.015. Epub 2017 Aug 2.

**The publisher's version is available at:**

<https://www.ncbi.nlm.nih.gov/pubmed/?term=10.1159%2F000490769>

**When citing, please refer to the published version.**

**Link to this full text:**

<http://hdl.handle.net/2318/1647996>

This full text was downloaded from iris-AperTO: <https://iris.unito.it/>

---

iris-AperTO

University of Turin's Institutional Research Information System and Open Access Institutional  
Repository

“How I treat” Autoimmune Diseases:

*State of the art on the management of rare rheumatic diseases with a special focus on ANCA-associated systemic idiopathic vasculitis.*

Dario Roccatello

1-Center of Research of Immunopathology and Rare Diseases -  
Coordinating Center of the Network for Rare Diseases of Piedmont  
and Aosta Valley, Department of Clinical and Biological Sciences and  
University of Turin

2-SCU Nephrology and Dialysis Unit, S. Giovanni Bosco Hospital and  
University of Turin, Turin, Italy

### **Corresponding Author**

Dario Roccatello, Center of Research of Immunopathology and Rare  
Diseases- Coordinating Center of the Network for Rare Diseases of  
Piedmont and Aosta Valley, and SCU Nephrology and Dialysis Unit,  
Department of Clinical and Biological Sciences, University of Turin,  
San Giovanni Hospital, Piazza del Donatore di Sangue 3, 10054,  
Turin, Italy.

Phone: +390112402056, Fax: +390112402052, Email:

dario.roccatello@unito.it

Keywords: autoimmune diseases, juvenile idiopathic arthritis, ANCA,  
vasculitis, Rituximab, idiopathic inflammatory myopathies, adult  
onset Still’s disease, systemic sclerosis



## Abstract

This Special Issue of *Autoimmunity Reviews* constitutes summaries of presentations at the 20th International Meeting on Immune Pathology and Orphan Diseases, held in Torino, Italy, 25-28<sup>th</sup> January 2017. As such, these presentations represent the state of the art on the pathophysiology of autoimmune diseases as well as the most recent insights into the management of these pathologic conditions. The latter includes both the optimal use of established drugs and approaches as well as novel knowledge on the means and consequences of targeted blocking of molecules or cellular mechanisms.

The 2nd Turin Congress on systemic idiopathic vasculitis concluded the works of the International Meeting on Immune Pathology and Orphan Diseases.

This Satellite Congress was mainly addressed to the management of antineutrophil cytoplasm antibody (ANCA)-associated vasculitis: advances on induction therapy and maintenance treatment. Guidelines and recommendations were critically discussed, reviewing available evidence providing experts' insights.

The papers in this Special Issue of Autoimmunity Reviews constitute summaries of presentations at the 20th International Meeting on Immune Pathology and Orphan Diseases, held in Torino, Italy, 25-28<sup>th</sup> January 2017. As such, these presentations represent the state of the art on the pathophysiology of autoimmune diseases as well as the most recent insights into the management of these pathologic conditions. The latter includes both the optimal use of established drugs and approaches as well as novel knowledge on the means and consequences of targeted blocking of molecules or cellular mechanisms.

Firstly, Cimaz and co-workers (1) focused on the treatment of juvenile idiopathic arthritis (JIA), reviewing the current therapeutic approaches and highlighting the unmet needs. The management of patients with JIA has significantly improved in the last 15 years due to the introduction of biologic agents and the development of large pediatric rheumatology research networks (e.g. Paediatric Rheumatology InterNational Trials Organisation (PRINTO), the -Pediatric Rheumatology Collaborative Study Group and the Childhood Arthritis & Rheumatology Research Alliance). Nevertheless, JIA treatment remains challenging, particularly in patients who fail to respond to the traditional agents and develop early bone erosions or in those who suffered for frequent relapses. Of interest, their review addresses hot topics in the management of JIA, including the safety issues related to the switch among biologics and provides the Authors' expert opinion about an important

unsolved question: when and how withdrawal biological therapy in patients with JIA.

Rossi and colleagues (2) explored current and novel approaches for the management of systemic sclerosis (SSc). The key message of their review is that while there is no curative therapy for scleroderma yet, there are several treatment options to improve both quality of life and survival of these patients. In this scenario, early detection of disease and immediate intervention appears to make a difference. It is important to appreciate that SSc is a highly heterogeneous disease with both clinical and laboratory predictors available to define expected disease course. Refined clinical phenotyping and careful early evaluation for active occult organ disease are the keys to deciding appropriate treatment approach.

The challenging management of idiopathic inflammatory myopathies (IIMs) is discussed by Cavagna and co-workers by reviewing the current available guidelines and by providing their expert opinion perspectives (3). They carried out a practical evaluation of the current status of treatment in patients affected by IIMs by highlighting unmet needs and focusing on established approaches. A detailed therapeutic algorithm summarizing available therapies and their potential areas of effectiveness has been discussed. However, taken together, the data confirm how further efforts are needed in order to improve and harmonize the therapeutic approach in patients with IIMs.



The management of Adult Onset Still's Disease (AOSD) is described by Govoni and colleagues (4). When putting together the available evidences, they concluded that the best therapy for AOSD has not yet been defined by recommendations or guidelines, and still relies on the personal clinical experience of the attending physician. Among the others, their main message relies on the importance of quickly achieving the clinical remission, especially in the systemic subset of the disease, once the diagnosis is confidently reached. While steroids and conventional DMARDs still remain the first line of therapy, the use of biologic DMARDs (Ab anti-IL1, anti-IL6 and anti-TNF) has proven to be useful and can allow physicians to obtain a complete and stable control of the disease when other therapies failed.

### **Special focus on ANCA-associated vasculitis**

The 2nd Turin Congress on systemic idiopathic vasculitis concluded the works of the International Meeting on Immune Pathology and Orphan Diseases. This Satellite Congress was mainly addressed to the management of antineutrophil cytoplasm antibody (ANCA)-associated vasculitis: advances on induction therapy and maintenance treatment.

ANCA-associated vasculitis include: Granulomatosis with Polyangiitis (GPA), Microscopic Polyangiitis (MPA), and Eosinophilic Granulomatosis with Polyangiitis (EGPA). Renal-limited ANCA-associated vasculitis is considered a kidney-limited form of MPA. Several studies demonstrated that these diseases have some pathogenic similarities but different genetic associations [5-11]. In

the last few years, treatment strategies have been gradually better defined, and several biologic agents have been studied, especially the monoclonal anti-CD20 antibody Rituximab, in induction [12, 13] and in maintaining [14] remission in severe GPA or MPA setting. Glucocorticoids remain the cornerstone of therapy for ANCA-associated vasculitides, but efforts are still ongoing in order to identify potent glucocorticoid-sparing agents. In detail, the initial dosage of glucocorticoids for patients with active and severe disease is usually 1 mg/kg/day prednisone-equivalent, usually preceded by 1 to 3 boluses of methylprednisolone (7.5 to 15 mg/kg/day). Presently, several centers aim to stop glucocorticoids at 6 months.

Cyclophosphamide and Rituximab, combined with glucocorticoids, are two main agents for remission induction in patients with severe GPA or MPA. These drugs can induce a partial response or a complete remission in >80% of patients. For patients with severe EGPA, data are too limited at this time to consider Rituximab only as a potential alternative to cyclophosphamide as a front line therapy, but several evidences pointed out that it could be effective in refractory cases [15]. Cyclophosphamide can be administered as intravenous pulses (boluses at regular intervals; 15 mg/kg, every 14 days for 1 month then every 3 weeks) or continuous oral tablets (2 mg/kg/day) with doses adjusted to the age and the glomerular filtration rate of the patient. Both administration routes are effective in achieving remission, but oral cyclophosphamide is associated

with an increased frequency of neutropenia and infections, possibly due to a higher cumulative dose, which is about 16 g compared with 8 g for “pulse” regimen for the 3-month duration therapy. Of note, the risk of infertility and late complications (i.e., cancers of bladder and skin, and lymphomas) is linked with the cumulative dose as well. However, the use of oral cyclophosphamide is associated with a lower subsequent relapse rate (20% instead of 40%) [16].

Rituximab is a chimeric monoclonal antiCD20 antibody, which induces a sustained peripheral B-cells depletion, through the specific binding of CD20 antigen on B-lymphocytes surface. Rituximab has been evaluated in two randomized trials (RAVE and RITUXVAS) and subsequently approved as an alternative to cyclophosphamide followed by azathioprine to treat severe forms of GPA and MPA in adults with a history of ANCA positivity [12,13]. In these two studies, Rituximab was found to be not inferior to cyclophosphamide in inducing remission at 6 months. The response to Rituximab, compared to cyclophosphamide, may be superior in relapsers who are Rituximab-naive and PR3-ANCA positive patients as compared to MPO-ANCA positive ones [12]. Thus, when choosing between Rituximab and cyclophosphamide, one should consider several potential indications to Rituximab, including relapsing disease, protecting fertility, refractory disease, poorly tolerated cyclophosphamide, malignancy risks, limiting exposure to cyclophosphamide, c-ANCA positive disease.

In addition, plasma exchange (7 sessions over 2 weeks) combined with induction treatment can be considered for patients with severe ANCA-associated vasculitis with active glomerulonephritis and/or alveolar hemorrhage, and as a rescue treatment for patients who did not satisfactorily respond to the induction therapy [17]. However, the benefits of this procedure in such patients have not been formally and completely demonstrated.

Following induction with cyclophosphamide (usually 3 or 6 months of therapy), patients who achieve clinical remission can be switched to a less toxic immunosuppressant for maintenance. The maintenance treatment should last at least 18–24 months [18]. The most commonly used maintenance agent is azathioprine (2 mg/day, orally) while mycophenolate mofetil was found to be associated with higher relapse rate. Previous studies with maintenance for 1–3 years showed that irrespective of the induction and maintenance regimen, the relapse rate in GPA could reach 51%–64% at 7 years [19]. The preliminary results of the European REMAIN trial, which compared 2 vs 4 years of maintenance with azathioprine, suggest that the continuation of therapy for 4 years may be associated with a lower relapse rate, in particular for patients with persistent ANCA positivity at remission.

The maintenance strategy following the Rituximab-based induction treatment currently lacks consensus. In the RAVE trial, a multicenter randomized double-blind study, no maintenance therapy was given after the fourth Rituximab infusion. The relapse rates at 18 months

were comparable between the Rituximab and the cyclophosphamide-azathioprine arms, but they remained at approximately 30% [12].

Therefore, several options are eligible following Rituximab-based induction therapy. Some groups suggested that re-treatment with Rituximab should be considered according to B-cells and/or CD19+ CD20+ lymphocytes count monitoring (with a repeat full course of four Rituximab infusions with B-lymphocyte reconstitution and/or ANCA reappearance or significant titer increase) [20]. At the same time, others reported the usefulness of a systematic maintenance infusions of Rituximab at regular intervals, every 6-12 months, independently of ANCA status or B-cells count and using different dosages [21,22]. The French Vasculitis Study Group MAINRITSAN trial, a prospective randomized open-label study to compare azathioprine and Rituximab (500 mg every 6 months) as a maintenance therapy following a glucocorticoid plus cyclophosphamide-based induction in GPA or MPA patients, found a lower rate of major relapses with Rituximab at 28 months (5.3% vs 29.3%) [23]. Another international study (RITAZAREM) is evaluating Rituximab, 1000 mg every 4 months, vs azathioprine as a maintenance therapy in relapsing ANCA-positive patients with GPA or MPA following a glucocorticoid plus Rituximab-based induction.

**How I treat patients in clinical practice:**

We have previously published the favorable outcome of 11 patients with severe AAV treated with an improved “4+2” Rituximab protocol [24]. This therapeutic approach was generally well tolerated and allowed to avoid further immunosuppressive maintenance therapy permitting tapering of oral prednisone to 5 mg/day by the end of the 3rd month after Rituximab administration. Its long-term safety profile has been demonstrated in a recent study [25] collecting data of patients followed for a mean of 85 months (range 45-132 months).

All patients given the “4+2” Rituximab protocol had a complete peripheral blood-B-cells depletion. The CD20+ B-cells were detectable in the circulation after a mean of 11.5 months (9-19 months). Of note, after 36 months, CD20+ cells count was still lower than baseline ( $p < 0.01$ ).

A single cycle of “4+2” Rituximab protocol was able to maintain in remission more than 60% of the patients for at least 5 years. In detail, following a single cycle “4+2” Rituximab protocol, 4 out of 11 patients (37%) remained in remission with no relapse (median 66 months [60-108]). Seven patients relapsed after a remission period of 54 months (24-96) and were similarly re-treated. Six months later, 6 of 7 (86%) were in complete remission, 1 (14%) in partial remission. After the second cycle of RTX these 7 patients had a complete remission over a median of 32 months (12-96) of observation.

The efficacy of the “4+2” dose protocol is probably related to a more effective tissue depleting activity when compared to the standard scheme, providing a more prolonged clinical remission.

As regard to the maintenance therapy, due to the delayed onset of relapse, this experience suggested that the policy of monitoring patients could be better than to administer fixed doses of RTX whatever the clinical assessment, especially in MPO-positive patients. Indeed, all 4 patients of our series relapsing in the first 5 years of follow-up after the first “4+2” Rituximab cycle were PR3 positive.

On the grounds of this experience we recently introduced in our Department a therapeutic algorithm based on clinical and histological presentation. Briefly, an intensified “4+2” Rituximab-protocol is administered to all patients with ANCA-associated vasculitis with biopsy-documented renal involvement. The protocol consists of 3 Methylprednisolone pulses of 15 mg/Kg together with 4 Rituximab infusions of 375 mg/m<sup>2</sup> weekly + 2 more doses at 1 and 2 months and oral corticosteroids 1 mg/kg tapered in 6 months. In those patient with serum creatinine levels higher than 5 mg/dl and more than 50% epithelial (florid) crescents at the renal biopsy (so called “crescentic forms”) 2 bolus dose (two weeks apart) of 15 mg/kg cyclophosphamide, adjusted for the renal impairment, are added to this regimen in order to potentiate the CD20+ B-cells depletion [16]. Plasma exchange (7 procedures) is performed in the presence of alveolar hemorrhage, renal rapidly progressive

impairment or dialysis dependence. No further immunosuppressive maintenance therapy is administered and corticosteroids are discontinued within the sixth month. CD20+ B-cells and ANCA are strictly monitored. In case of CD20+ cells re-population and ANCA increase (“biochemical flare”), a maintenance regimen of Rituximab 500 mg every 4 months for 2 years followed by 500 mg every 6 months for 1 year has been envisaged. A re-induction therapy with 4 Rituximab infusions of 375 mg/m<sup>2</sup> weekly (instead of 6) and a faster tapering of oral corticosteroids (aimed to discontinue the drug within the third month) has been reserved to the case of frank clinical relapse.

This protocol has been already applied to 12 MPA patients with mean serum creatinine levels of 5.8 mg/dl. Patients were meanly followed for 14 months. At 6 months, 4 of them (3 having >50% florid crescents and 1 with advanced, i.e., > 50%, glomerular global sclerosis) were in dialysis. Eight patients (3 with >50% and 5 with <50% florid crescents, including one case having >50% glomerular sclerosis) were hemodialysis-free and in clinical remission. Four GPA patients were followed for 19 months. One of 2 patients having >50% florid crescents, who were oliguric at baseline, remained in dialysis at the sixth month of observation. All 4 GPA patients reached a complete remission of extra-renal involvement with disappearance of constitutional symptoms.

### **Concluding remarks**



These are only few of the aspects discussed during the Meeting, in which all the participants were actively involved in vibrant debates.

It seems clear that what will be in the future seems to be now at our door, with

novel targeted therapies and the upcoming personalized medicine vigorously knocking. Yet, in this crucial moment, we should learn how to better use the “old” weapons. While a growing body of evidence coming from randomized control trials has recently paved the way for the dissemination of guidelines and recommendation, the management of rare, systemic, chronic autoimmune disease is still challenging and suffers for unsolved questions.

This is where the real-world data and the opinion of experts have a role to play and the rationale behind the “How I treat” approach applied in this issue.

Evidence-based medicine has placed a general priority on knowledge gained from clinical research for clinical decision-making. However, knowledge derived from empiric, population-based research, while valued for its ability to limit bias, is not directly applicable to the care of individual patients. The gap between clinical research and individual patient care centers on the fact that empiric research is not generally designed to answer questions of direct relevance to individual patients. Clinicians must use other forms of medical knowledge, including pathophysiologic rationale and clinical experience, in order to achieve the best medical decision for a specific patient. In addition, physicians must elucidate

and account for the goals and values of individual patients as well as barriers and facilitators of care inherent in the system in which they practice. In a complex field such as the management of autoimmune evidence-based guidelines have to be filtered by the prescribing physicians' clinical judgment, negotiating potentially conflicting warrants for action, in an effort to arrive at the best decision for a particular patient.

### **Acknowledgements**

The Guest Editor is grateful to all who contributed to the success of the 20th International Meeting on Immune Pathology and Orphan Diseases. He would like to thank all of participants who have actively contributed to the discussions and the speakers for their excellent presentations. Thanks to the members of the Organizing Committee for their invaluable help.

The conference was organized under the responsibility of the Center of Research of Immunopathology and Rare Diseases-Coordinating Center of the Network for Rare Diseases of Piedmont and Aosta Valley, and SCU Nephrology and Dialysis Unit, Department of Clinical and Biological Sciences, University of Turin, Italy and in collaboration with an International advisory board consisting of colleagues from departments of rheumatology, immunology and nephrology of several US and European universities.

- [1] Cimaz R, Marino A, Alberto Martini A, How I Treat Juvenile Idiopathic arthritis: a state of the art review. *Autoimmunity Reviews*, 2017, in press
- [2] Rossi D, Zanatta E, Marson P, Sciascia S, Polito P, Roccatello D, Cozzi F. How i treat patients with systemic sclerosis in clinical practice. *Autoimmunity Reviews*, 2017, in press.
- [3] Cavagna L, Monti S, Caporali R, Gatto M, Iaccarino L, Doria A. How I treat idiopathic patients with inflammatory myopathies in the clinical practice. *Autoimmunity Reviews*, 2017, in press.
- [4] Govoni M, Bortoluzzi A, Rossi D, Modena V. How I treat patients with Adult Onset Still's Disease in clinical practice. *Autoimmunity Reviews*, 2017, in press.
- [5] Kronbichler A, Windpessl M, Pieringer H, Jayne DRW. Rituximab for immunologic renal disease: What the nephrologist needs to know. *Autoimmun Rev.* 2017;16:633-643.
- [6] Cottin V, Bel E, Bottero P, Dalhoff K, Humbert M, Lazor R, Sinico RA, Sivasothy P, et al. Revisiting the systemic vasculitis in eosinophilic granulomatosis with polyangiitis (Churg-Strauss): A study of 157 patients by the Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires and the European Respiratory Society Taskforce on eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *Autoimmun Rev.* 2017;16:1-9.
- [7] Jarrot PA, Kaplanski G. Pathogenesis of ANCA-associated vasculitis: An update. *Autoimmun Rev.* 2016;15:704-13.

- [8] Csernok E, Damoiseaux J, Rasmussen N, Hellmich B, van Paassen P, Vermeersch P, Blockmans D, Cohen Tervaert JW, Bossuyt X. Evaluation of automated multi-parametric indirect immunofluorescence assays to detect anti-neutrophil cytoplasmic antibodies (ANCA) in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). *Autoimmun Rev.* 2016;15:736-41.
- [9] Iannella G, Greco A, Granata G, Manno A, Pasquariello B, Angeletti D, Didona D, Magliulo G. Granulomatosis with polyangiitis and facial palsy: Literature review and insight in the autoimmune pathogenesis. *Autoimmun Rev.* 2016;15:621-31.
- [10] Kallenberg CGM. Pathogenesis of ANCA-associated vasculitides. *Ann Rheum Dis* 2011;70 Suppl 1:i59-63.  
doi:10.1136/ard.2010.138024.
- [11] Xie G, Roshandel D, Sherva R, Monach PA, Lu EY, Kung T, et al. Association of granulomatosis with polyangiitis (Wegener's) with HLA-DPB1\*04 and SEMA6A gene variants: evidence from genome-wide analysis. *Arthritis Rheum* 2013;65:2457-68.  
doi:10.1002/art.38036.
- [12] Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med* 2013;369:417-27.  
doi:10.1056/NEJMoa1213277.
- [13] Jones RB, Cohen Tervaert JW, Hauser T, Luqmani R, Morgan MD,

- Peh CA, et al. Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis. *N Engl J Med* 2010;363:211–20. doi:10.1056/NEJMoa0909169.
- [14] Charles P, Neel A, Tieulie N, Hot A, Pugnet G, Decaux O, et al. Rituximab for induction and maintenance treatment of ANCA-associated vasculitides: a multicentre retrospective study on 80 patients. *Rheumatology* 2014;53:532–9. doi:10.1093/rheumatology/ket381.
- [15] Roccatello D, Sciascia S, Rossi D, Alpa M, Naretto C, Russo A, et al. Long-term effects of rituximab added to cyclophosphamide in refractory patients with vasculitis. *Am J Nephrol* 2011;34:175–80. doi:10.1159/000329535.
- [16] Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis* 2012;71:955–60. doi:10.1136/annrheumdis-2011-200477.
- [17] de Joode AAE, Sanders JSF, Smid WM, Stegeman CA. Plasmapheresis rescue therapy in progressive systemic ANCA-associated vasculitis: single-center results of stepwise escalation of immunosuppression. *J Clin Apher* 2014;29:266–72. doi:10.1002/jca.21318.
- [18] Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JWC, Dadoniené J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic

- autoantibodies. *N Engl J Med* 2003;349:36–44.  
doi:10.1056/NEJMoa020286.
- [19] Springer J, Nutter B, Langford CA, Hoffman GS, Villa-Forte A. Granulomatosis With Polyangiitis (Wegener’s). *Medicine (Baltimore)* 2014;93:82–90.  
doi:10.1097/MD.0000000000000020.
- [20] Cartin-Ceba R, Golbin JM, Keogh KA, Peikert T, Sánchez-Menéndez M, Ytterberg SR, et al. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener’s): Ten-year experience at a single center. *Arthritis Rheum* 2012;64:3770–8.  
doi:10.1002/art.34584.
- [21] Jones RB, Ferraro AJ, Chaudhry AN, Brogan P, Salama AD, Smith KGC, et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2009;60:2156–68.  
doi:10.1002/art.24637.
- [22] Roubaud-Baudron C, Pagnoux C, Méaux-Ruault N, Grasland A, Zoulim A, LE Guen J, et al. Rituximab maintenance therapy for granulomatosis with polyangiitis and microscopic polyangiitis. *J Rheumatol* 2012;39:125–30. doi:10.3899/jrheum.110143.
- [23] Guillevin L, Pagnoux C, Karras A, Khouatra C, Au-maitre O, Cohen P et al. Rituximab versus Aza-thioprine for Maintenance in ANCA-Associated Vasculitis [Abstract]. *Arthritis Rheum* 2012:S706.

- [24] Roccatello D, Sciascia S, Rossi D, Alpa M, Naretto C, Radin M, et al. The “4 plus 2” rituximab protocol makes maintenance treatment unneeded in patients with refractory ANCA-associated vasculitis: A 10 years observation study. *Oncotarget* 2017;5. doi:10.18632/oncotarget.18120.
- [25] Roccatello D, Sciascia S, Baldovino S, Rossi D, Alpa M, Naretto C, et al. A 4-year observation in lupus nephritis patients treated with an intensified B-lymphocyte depletion without immunosuppressive maintenance treatment-Clinical response compared to literature and immunological re-assessment. *Autoimmun Rev* 2015. doi:10.1016/j.autrev.2015.07.017.