


ORIGINAL RESEARCH

Tolerance and efficacy of targeted therapies prescribed for off-label indications in refractory systemic autoimmune diseases: data of the first 100 patients enrolled in the TATA registry (TARgeted Therapy in Autoimmune Diseases)

Jacques-Eric Gottenberg ^{1,2} Aurore Chaudier,^{1,2} Yves Allenbach ^{3,4} Arsène Mekinian ⁵ Zahir Amoura,^{6,7} Patrice Cacoub,^{4,8} Divi Cornec ^{9,10} Eric Hachulla ^{11,12} Pierre Quartier,^{13,14} Isabelle Melki ^{15,16} Christophe Richez ^{17,18} Raphaelae Seror ^{19,20} Benjamin Terrier ^{4,21} Valérie Devauchelle-Pensec,^{9,10} Julien Henry,^{19,20} Marc Gatfosse,²² Laurence Bouillet,²³ Emeline Gaigneux,²⁴ Vincent Andre,²⁴ Gildas Baulier,²⁵ Aurélie Saunier,²⁵ Marie Desmurs,²⁶ Antoine Poulet,²⁷ Mathieu Ete,²⁸ Boris Bienvenu,²⁷ Marie-Elise Truchetet ^{18,29} Martin Michaud,³⁰ Claire Larroche,³¹ Azeddine Dellal,³² Amélie Leurs,³³ Sebastien Ottaviani,³⁴ Hubert Nielly ³⁵ Guillaume Vial,³⁶ Roland Jaussaud,³⁷ Bénédicte Rouvière,³⁸ Pierre-Yves Jeandel,³⁹ Aurelien Guffroy,^{2,40} Anne-Sophie Korganow,^{2,40} Mathieu Jouvray,³⁵ Alain Meyer ^{1,2} Emmanuel Chatelus,^{1,2} Christelle Sordet,^{1,2} Renaud Felten ^{1,2} Jean Sibilia,^{1,2} Samira Litim-Ahmed-Yahia,¹ Jean-Francois Kleinmann ^{1,2} Xavier Mariette ^{19,20}

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For numbered affiliations see end of article.

Correspondence to

Dr Jacques-Eric Gottenberg; jacques-eric.gottenberg@chru-strasbourg.fr

ABSTRACT

Objectives To assess the tolerance and efficacy of targeted therapies prescribed off-label in refractory low-prevalence autoimmune and inflammatory systemic diseases.

Methods The TATA registry (TARgeted Therapy in Autoimmune Diseases) is a prospective, observational, national and independent cohort follow-up. The inclusion criteria in the registry are as follows: age >18 years; low-prevalence autoimmune and inflammatory systemic disease treated with off-label drugs started after 1 January 2019.

Results Hundred (100) patients (79 women) were enrolled. The median age was 52.5 years (95% CI 49 to 56) and the median disease duration before enrolment was 5 years (3 to 7). The targeted therapies at enrolment were as follows: Janus kinase/signal transducers and activators of transcription inhibitors (44%), anti-interleukin (IL)-6R (22%), anti-IL-12/23, anti-IL-23 and anti-IL-17 (9%), anti-B cell activating factor of the tumour necrosis factor family (5%), abatacept (5%), other targeted treatments (9%) and combination of targeted treatments (6%). 73% of patients were receiving corticosteroid therapy at enrolment (median

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In France, the management of low-prevalence autoimmune and inflammatory systemic diseases benefits from a network of reference centres, through which clinician experts provide guidance for therapeutic decisions in refractory diseases that might include off-label drugs, generally fully reimbursed.

WHAT THIS STUDY ADDS

⇒ Our study reports the initial results of the TATA registry and confirms the diversity of targeted treatments, prescribed off-label and their corticosteroid-sparing effect when effective, with an acceptable safety profile, in refractory autoimmune diseases.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Inclusion and follow-up in this register will grow up in the coming years. We hope these results will pave the way to a European collaborative registry of off-label drugs in refractory autoimmune diseases.

dose 10 mg/day). The current median follow-up time is 9 months (8 to 10).

Safety: 11 serious infections (incidence rate of 14.8/100 patient-years) and 1 cancer (1.3 cancers/100 patient-years) were observed. Two patients died from severe COVID-19 (2.7 deaths/100 patient-years).

Efficacy: the targeted treatment was considered effective by the clinician in 56% of patients and allowed, in responders, a median reduction of oral corticosteroids of 15 (9 to 21) mg/day, below 7.5 mg/day in 76% of patients, while 28% discontinued.

Conclusion These initial results of the TATA registry confirm the diversity of targeted treatments prescribed off-label in refractory autoimmune diseases and their corticosteroid-sparing effect when effective. Tolerance was acceptable in these refractory patients with a long history of treatment with immunosuppressive drugs.

INTRODUCTION

Low-prevalence autoimmune and inflammatory systemic diseases are particularly disabling and without specific treatment for most of them. However, these diseases share common pathophysiological mechanisms with rheumatoid arthritis (RA), spondyloarthritis (SpA) or haematological malignancies. These latter diseases have a large therapeutic arsenal including numbers of targeted treatments. The low prevalence of systemic autoimmune diseases (AIDs) and the diversity of their clinical manifestations make complex to conduct randomised clinical trials to assess the potential efficacy of targeted treatments.

In France, the management of these diseases benefits from a network of reference centres, through which clinician experts provide guidance for therapeutic decisions in refractory diseases that might include off-label drugs, generally fully reimbursed. Thanks to such an organisation, we previously set up different registries that have shown that the off-label use of anti-tumour necrosis factor (TNF) or rituximab,^{1,2} in some refractory corticosteroid-dependent systemic AIDs, could be useful.

We therefore established a national, prospective registry to analyse the tolerability and efficacy of off-label targeted treatments prescribed in refractory low-prevalence autoimmune and inflammatory systemic disease. Here, we present the results of the first 100 patients enrolled in the TATA (TArgeted Therapy in Autoimmune Diseases) registry.

PATIENTS AND METHODS

Patients

The TATA registry is a prospective, observational, national and independent registry set-up on the umbrella of the French Society for Rheumatology (SFR), the French National Society for Internal Medicine (SNFMI) and the 'Filière des maladies auto-immunes et auto-inflammatoires rares' (FAI²R) and 'Immune-Mediated Inflammatory Diseases Alliance for Translational and Clinical Research' (IMIDIATE) networks and sections 'Club Rhumatismes et Inflammation' (CRI).

The inclusion criteria in the registry are as follows: age >18 years; low-prevalence autoimmune and inflammatory systemic disease (systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, inflammatory myopathy, vasculitis, etc) or other refractory rheumatism treated with off-label drugs started after 1 January 2019.

Exclusion criteria were treatment with TNF inhibitors or rituximab, targeted treatments for which numerous off-label data are already available.

The decision to start the targeted treatment was made by the clinician in charge of the patient, who was advised to seek the expert advice of a national reference or competence centre for low-prevalence autoimmune and inflammatory systemic disease.

All physicians in reference centres were asked to enrol patients in the TATA registry. The SFR and SNFMI, their network (FAI²R, IMIDIATE) and section (CRI), sent information emails twice a year on the inclusion criteria and on the number of patients enrolled.

Methods

The data were collected in a standardised fashion using an electronic case report form (<https://cgfl.ennov.com/CSOnline>) with a proposed follow-up frequency at 3 months, 6 months, then every 6 months or earlier in case of serious adverse event or withdrawing or changing the targeted treatment. The patient continued to be followed up 1 year after the discontinuation of the last off-label targeted treatment. The data concerning serious infections (resulting in death, hospitalisation or intravenous antiviral or antibiotic treatment), cancer and death were confirmed by checking the medical chart. The efficacy of the targeted treatment was assessed by the targeted drug retention rate, the corticosteroid-sparing effect and the clinician's evaluation.

Statistical analysis

The data are presented as a median (CI) for continuous variables and as a value (proportion) for qualitative variables. Incidence rates of serious infections and cancers are reported.

RESULTS

Patients' characteristics

Of the first 100 patients enrolled in the TATA registry between 01 January 2019 and 29 June 2021, 79% were female.

The median age was 52.5 years (49 to 56) and the median disease duration was 5 years (3 to 7).

Diseases included in the registry were as follows: inflammatory myopathy (24%), systemic sclerosis (13%), Sjögren's syndrome (15%), vasculitis (15%), systemic lupus erythematosus (11%) and other refractory rheumatism (22%) (table 1).

Reasons for initiating the off-label targeted treatment

Previous therapeutic regimens included corticosteroids and classic synthetic immunomodulatory drugs in 91%

Table 1 Clinical characteristics of the first 100 patients enrolled in the TATA registry

	Number	95% CI
Number of patients enrolled	100	
Age (years)	52.5	49 to 56
Sex (female/100)	79	
Disease duration before enrolment (median, years)	5	3 to 7
Diagnosis at enrolment		
Systemic lupus erythematosus	11	
Primary and associated Sjögren's syndrome*	15	
Systemic sclerosis	13	
Inflammatory myositis	24	
Large-vessel and other vasculitis	15	
Other refractory rheumatism†	22	
Targeted therapies prescribed as first line		
JAK/STAT inhibitors	44	
Anti-IL-6R	22	
Anti-IL-12/23, anti-IL-23 and anti-IL-17	9	
Anti-BAFF	5	
Abatacept	5	
IL-1Ra	4	
Anti-CD20	2	
Nintedanib/ibrutinib	2	
Anti-IL-17	1	
Anti-CD38	1	
Combination of targeted treatments‡	6	
Immunomodulator co-treatment		
Methotrexate	34	
Hydroxychloroquine	23	
IV immunoglobulin	6	
Mycophenolate mofetil	4	
Azathioprine	3	
Tacrolimus	2	
Cyclophosphamide	2	
Leflunomide	1	
Corticosteroids at enrolment		
Dose (median, mg/day)	10	5 to 15

*Eleven cases of primary Sjögren's syndrome and three cases of associated Sjögren's syndrome.

†One case of unclassified connective tissue disease with arthralgias, skin lesions and antinuclear antibodies without specificity, four cases of overlap syndrome (myositis+rheumatoid arthritis+Sjögren's syndrome; rheumatoid arthritis+myositis; rheumatoid arthritis+systemic sclerosis; rheumatoid arthritis+haemolytic autoimmune anaemia), one case of polymyalgia rheumatica, five cases of axial and peripheral spondylarthritis, one case of SAPHO syndrome (an acronym for synovitis, acne, pustulosis, hyperostosis, osteitis), three cases of Still's disease, two cases of idiopathic pericarditis, one case of unclassified autoinflammatory syndrome, one case of sarcoidosis, one case of polyarticular chondrocalcinosis, two cases of rheumatoid arthritis.

‡Four anti-BAFF+anti-CD20 (rituximab), one nintedanib+anti-IL-6R, one nintedanib+anti-CD20 (rituximab).
BAFF, B cell activating factor of the tumour necrosis factor family; IL, interleukin; IV, intravenous; JAK/STAT, Janus kinase/signal transducers and activators of transcription; TATA, TArgeted Therapy in Autoimmune Diseases.

of patients. Forty-five per cent of patients had also been previously treated with at least one targeted therapy. Reason for initiating the off-label targeted treatment was a refractory disease in all patients. Fourteen per cent of patients also had a life-threatening presentation. Specific disease manifestations that led to the off-label treatments are summarised in online supplemental table 1.

Targeted therapies prescribed at enrolment and immunomodulator co-treatment

At enrolment in the registry, 44% of patients received Janus kinase/signal transducers and activators of transcription (JAK/STAT) inhibitors (28 of 44 baricitinib, 13 of 44 tofacitinib, 2 of 44 upadacitinib, 1 of 44 ruxolitinib), 22% of patients received anti-interleukin (IL)-6R (21 of 22 tocilizumab, 1 of 22 sarilumab), 9% of patients received anti-IL-12/23, anti-IL-23 or anti-IL-17 (7 ustekinumab, 1 guselkumab, 1 ixekizumab), 5% of patients received anti-B cell activating factor of the tumour necrosis factor family (BAFF) (belimumab), 5% of patients received abatacept, 2% of patients received non-rituximab anti-CD20 (obinutuzumab), 1% anti-CD38 (daratumumab), 4% IL-1Ra, 2% tyrosine kinase inhibitors (ibrutinib and nintedanib), 6% a combination of targeted therapies: 4 anti-BAFF and anti-CD20 combinations, and, in 2 patients, nintedanib combined either with anti-IL-6R or anti-CD20 (rituximab). Seventy-three per cent of patients were receiving corticosteroids at the start of the targeted therapy at a median dose of 10 (5 to 15) mg/day. Sixty-five patients (65%) had an associated classic synthetic immunomodulatory drug (table 1).

Safety

Ninety-nine (99) patients out of 100 had undergone at least one follow-up visit at the date of analysis (29 August 2021). The median follow-up time was 9 months (8 to 10) (74 patient-years).

The results concerning safety of targeted therapies are summarised in table 2.

Eleven patients had a serious infection (incidence rate of 14.8 serious infections/100 patient-years) (table 2), of which two patients died (2.7 deaths/100 patient-years). These two patients had primary Sjögren's syndrome complicated by severe cryoglobulinaemia vasculitis: one patient died from severe COVID-19 5 months after the introduction of treatment with obinutuzumab; one patient died from severe COVID-19 and septic shock with *Enterobacter cloacae* 18 months after the introduction of treatment with belimumab combined with rituximab.

Two patients had an opportunistic infection (2.7/100 patient-years): a first patient with anti-Jo1 syndrome and associated Sjögren's syndrome had tenosynovitis with atypical mycobacteria (*Mycobacterium malmoense*) while being treated for 2 months with a combination of belimumab and rituximab; another patient, with anti-MDA5 myopathy had cytomegalovirus necrotising retinitis 7 months after the introduction of baricitinib combined with corticosteroids and tacrolimus.

Table 2 Serious adverse events

Pathology	Age	Sex	Targeted therapy	Time to onset after introduction (months)	Co-treatment	Serious adverse events
Primary Sjögren's syndrome	65	F	Obinutuzumab	5	CS 5 mg/day+HCQ	Severe COVID-19, death
Primary Sjögren's syndrome	74	F	Belimumab+rituximab	18	CS 5 mg/day+HCQ	Urinary septic shock (post-COVID-19 context), death
Systemic sclerosis	63	M	Tocilizumab	2	MTX	Sepsis with <i>Staphylococcus epidermidis</i>
Primary Sjögren's syndrome	74	F	Belimumab	11	CS 5 mg/day+HCQ	Septic shock in a context of neutropenia (not documented)
Anti-TIF1 gamma myopathy	42	M	Baricitinib	7	CS 30 mg/day+IVIg	Perforated diverticulitis
Anti-NXP2 myopathy	47	F	Baricitinib	5	CS 5 mg/day	Scapular abscess with surgical debridement
Systemic lupus erythematosus+anti-TIF1 gamma	69	F	Belimumab	2	CS 9 mg/day	Severe gastrointestinal infection with <i>Campylobacter jejuni</i>
Behçet's	31	M	Baricitinib	2	None	Toxic pancytopenia
Behçet's	47	F	Tocilizumab	1	CS 15 mg/day+MTX+COL	Malignant otitis with <i>Pseudomonas aeruginosa</i>
Sjögren's syndrome+anti-Jo1	27	F	Belimumab+rituximab	2	CS 7.5 mg/day+MTX	Tenosynovitis with <i>Malmoense mycobacteria</i>
Anti-MDA5 myositis	56	F	Baricitinib	7	CS 30 mg/day+tacrolimus	Necrotising CMV retinitis of the right eye
Systemic lupus erythematosus	29	F	Tofacitinib	4	CS 5 mg/day+HCQ+AZA	Cutaneous T cell lymphoma recurrence

AZA, azathioprine; CMV, cytomegalovirus; COL, colchicine; CS, corticosteroids; HCQ, hydroxychloroquine; IVig, intravenous immunoglobulin; MTX, methotrexate.

One patient (1.3 cancers/100 patient-years) with systemic lupus erythematosus had a recurrence of cutaneous T cell lymphoma after 6 months of tofacitinib combined with azathioprine.

No major adverse cardiovascular event (MACE) was reported.

Efficacy data

Last evaluation of efficacy was performed between enrolment and 3 months for 18% of patients, 3 and 6 months for 33%, 6 and 12 months for 26%, and after 12 months for 22% of patients. The targeted treatment was considered to be efficient by clinicians in 56 out of 99 patients (56%): in 8 of 11 (73%) patients with lupus, in 6 of 15 (40%) patients with Sjögren's syndrome, in 10 of 13 (77%) patients with systemic sclerosis, in 15 of 24 (62.5%) patients with inflammatory myopathy, in 6 of 15 (40%) patients with vasculitis, and in 11 of 22 (50%) patients with another refractory inflammatory rheumatism.

Out of the 99 patients with at least one follow-up visit, 43 patients (43%) had to discontinue the targeted therapy prescribed at enrolment. Thirty-two of 43 (74%) discontinued the targeted therapy due to inefficacy, 9 of 43 due to adverse effects (21%) including 2 of 43 (5%) due to a serious adverse event. Treatment was discontinued for disease remission in one patient and in one patient for planning a pregnancy.

Forty-three patients were responders out of 73 patients treated with oral corticosteroids at enrolment. In responders, the median reduction of corticosteroids was 15 (9 to 21) mg/day. Thirty-eight out of 43 patients were treated with a daily dose of oral corticosteroids ≥ 7.5 mg/day at enrolment. Twenty-nine out of 38 patients (76%) with an initial dose ≥ 7.5 mg/day were able to reduce corticosteroids to below 7.5 mg/day. Twelve of 43 responders treated with oral corticosteroids at enrolment (28%) were able to completely discontinue oral corticosteroids.

DISCUSSION

Our study reports the initial results of the TATA registry and confirms the potential interest of using off-label targeted treatments in various refractory AIDs. Despite the limited number of patients enrolled to date, we consider it important to share these initial results quickly while continuing enrolment.

One of the limits of our study is related to its observational and pragmatic nature. We therefore do not have data concerning disease activity scores for most patients. However, this study enabled us to gather safety, efficacy data according to the clinician, therapeutic maintenance and corticosteroid-sparing effect. Of note, we confirmed serious adverse events by individually examining each patient chart concerned.

It is important to note that this registry meets many needs and might provide guidance to clinicians for refractory patients with autoimmune or inflammatory systemic disease. A formal and consensus definition

of a refractory disease is not available for each of these diseases. In the TATA registry, clinicians considered their patients as refractory because they all failed corticosteroids and immunosuppressants, and, for nearly half of them, a previous targeted therapy. In refractory autoimmune and inflammatory systemic diseases, clinicians might consider the use of targeted therapies^{3 4} that are approved for RA, SpA or haematological malignancies, given that all these diseases share some commonalities in their immunopathogenesis.

However, not every targeted treatment for each low-prevalence disease can be evaluated by a randomised clinical trial. This possibility of a clinical trial is even more unrealistic for overlap syndromes and other refractory inflammatory diseases, which represent a quarter of enrolments in the registry. When data from randomised trials are lacking or very limited, it is even more important to obtain real-life data from registries, with a specific focus on safety.

Concerning safety, the incidence rate of serious infections (14.8/100 patient-years) is higher than in approved indications particularly in RA (3–5/100 patient-years)⁵ or SpA. This difference is expected given the higher initial doses of corticosteroids (median dose of 10 mg/day in the TATA registry) than in RA or SpA, and the multirefractory nature of the pathologies of these patients heavily pretreated with immunosuppressors. The two patients who died had been treated with anti-CD20 (obinituzumab and combination of rituximab and belimumab) and died from COVID-19, a disease in which it is well known that the risk of hospitalisation and death is highly increased by anti-CD20 or corticosteroids ≥ 10 mg/day.^{6 7} A longer follow-up is mandatory to allow a relevant analysis of the risk of cancer and MACE, which was recently reported to be associated with tofacitinib.⁸

Concerning efficacy, the targeted therapy has a corticosteroid-sparing effect in responders. This reduction in oral corticosteroid therapy probably mitigates the risk of infection subsequently associated with the targeted therapy, although this remains to be confirmed by extending the follow-up in the registry.

Finally, this registry also has the benefit of providing a 'snapshot' of the practices of clinicians towards refractory systemic AIDs. In the TATA registry, prescriptions, which were for the most part discussed collectively with experts at reference and competence centres, relied on advances in the understanding of AIDs (pathogenic roles of interferon signature, BTK, plasmacytes, etc), and the initial data in literature regarding JAK/STAT inhibitors in systemic lupus erythematosus⁹ and in myopathies¹⁰ or daratumumab in systemic lupus erythematosus.¹¹ Finally, it is important to note the innovative and rational nature of combined targeted treatments prescribed to act on several components of systemic AIDs: potential synergy of combining BAFF inhibition and B cell depletion¹² or of dual targeting of immunity and fibrosis.

CONCLUSION

These initial results of the TATA registry confirm the diversity of targeted treatments prescribed off-label in refractory AIDs and their corticosteroid-sparing effect if effective. Efficacy occurred in more than half of the patients with an acceptable safety profile. For patients and clinicians, it is now important to extend this prospective follow-up to confirm these initial findings and the acceptability of the benefit/risk ratio of off-label targeted therapies in patients with cortico-dependent systemic AIDs refractory to numerous previous conventional immunosuppressants.

Author affiliations

- ¹Rheumatology, Hôpitaux universitaires de Strasbourg, Strasbourg, France
- ²Rheumatology, East and South-West Reference Center, Strasbourg, France
- ³Department of Internal Medicine and Clinical Immunology, Hospital University Department: Inflammation, Immunopathology and Biotherapy (DHU i2B), University Hospital Pitié Salpêtrière, Paris, France
- ⁴Internal Medicine, Ile-De-France Reference Center, Paris, France
- ⁵Service de Médecine Interne, DHU i2B, Hospital Saint-Antoine, Paris, France
- ⁶Internal Medicine, University Hospital Pitié Salpêtrière, Paris, France
- ⁷Internal Medicine, Lupus and SAPL Reference Center, Paris, France
- ⁸Service de médecine interne et immunologie clinique, Hôpital Pitié-Salpêtrière, Paris, France
- ⁹Rhumatologie, Cavale Blanche Hospital, Brest, France
- ¹⁰Rheumatology, North and North-West Reference Center, Brest, France
- ¹¹Internal Medicine, Lille University School of Medicine, Lille, France
- ¹²Internal Medicine, North and North-West Reference Center, Lille, France
- ¹³Pediatric Immuno-Hematology and Rheumatology Unit, Hôpital universitaire Necker-Enfants malades, Paris, France
- ¹⁴Paediatric, RAISE Reference Center, Paris, France
- ¹⁵Laboratory of Neurogenetics and Neuroinflammation, Imagine Institute, Paris, France
- ¹⁶General Paediatrics, Infectious Diseases and Internal Medicine, Hôpital Universitaire Robert Debre, Paris, France
- ¹⁷Service de Rhumatologie, CHU Bordeaux GH Pellegrin, Bordeaux, France
- ¹⁸Rheumatology, East and South-West Reference Center, Bordeaux, France
- ¹⁹Rheumatology, Hôpital Bicêtre, Le Kremlin-Bicêtre, France
- ²⁰Rheumatology, Ile-De-France Reference Center, Le Kremlin-Bicêtre, France
- ²¹Internal Medicine, Hospital Cochin, Paris, France
- ²²Médecine Interne, Hôpital Saint-Antoine, Paris, France
- ²³Internal Medicine, University Hospital Centre Grenoble Alpes, Grenoble, France
- ²⁴Rheumatology, Centre Hospitalier Départemental Vendée, La Roche-sur-Yon, France
- ²⁵Internal Medicine, Centre Hospitalier de Périgueux, Périgueux, France
- ²⁶Rheumatology, Hospital Emile Muller, Mulhouse, France
- ²⁷Internal Medicine, Saint Joseph Hospital, Marseille, France
- ²⁸Saint Joseph Hospital, Marseille, France
- ²⁹Rheumatology, University Hospital Centre Bordeaux, Bordeaux, France
- ³⁰Internal Medicine, Hôpital Joseph Ducuing, Toulouse, France
- ³¹Service de médecine interne, Hôpital Avicenne, Bobigny, France
- ³²Rheumatology, Groupe Hospitalier Intercommunal Le Raincy-Montfermeil, Montfermeil, France
- ³³Internal Medicine, Centre Hospitalier de Dunkerque, Dunkerque, France
- ³⁴Rheumatology, Hôpital Bichat-Claude-Bernard, Paris, France
- ³⁵Internal Medicine, Begin Armed Forces Training Hospital, Paris, France
- ³⁶Department of Internal Medicine and Clinical Immunology, CHU de Bordeaux, Bordeaux, France
- ³⁷Barbois Hospital, Vandoeuvre-les-Nancy, France
- ³⁸Internal Medicine, Cavale Blanche Hospital, Brest, France
- ³⁹Service de Médecine Interne, University Hospital Centre Nice, Nice, France
- ⁴⁰Internal Medicine, Hôpitaux universitaires de Strasbourg, Strasbourg, France

Twitter Christophe Richez @crichez33

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Contributors JE-G is the author responsible for the overall content as the guarantor. The TATA registry is set up on the umbrella of the French Society for Rheumatology (SFR), the French National Society for Internal Medicine (SNFMI) and the 'Filière des maladies auto-immunes et auto-inflammatoires rares' (FAI²R) and 'Immune-Mediated Inflammatory Diseases Alliance for Translational and Clinical Research' (IMIDIATE) networks and sections 'Club Rhumatismes et Inflammation' (CRI), which have contributed to this work by identifying physicians to enrol patients and by sending information emails twice a year on the inclusion criteria and on the number of patients enrolled.

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ORCID iDs

Jacques-Eric Gottenberg <http://orcid.org/0000-0002-9469-946X>
 Yves Allenbach <http://orcid.org/0000-0002-3185-7993>
 Arsène Mekinian <http://orcid.org/0000-0003-2849-3049>
 Divi Cornec <http://orcid.org/0000-0002-9159-702X>
 Eric Hachulla <http://orcid.org/0000-0001-7432-847X>
 Isabelle Melki <http://orcid.org/0000-0002-8057-333X>
 Christophe Richez <http://orcid.org/0000-0002-3029-8739>
 Raphaele Seror <http://orcid.org/0000-0002-5523-1856>
 Benjamin Terrier <http://orcid.org/0000-0001-6612-7336>
 Marie-Elise Truchetet <http://orcid.org/0000-0001-8045-0180>
 Hubert Nielly <http://orcid.org/0000-0002-8042-5716>
 Alain Meyer <http://orcid.org/0000-0003-0893-6041>
 Renaud Felten <http://orcid.org/0000-0002-4951-4032>
 Jean-Francois Kleinmann <http://orcid.org/0000-0001-9062-7883>
 Xavier Mariette <http://orcid.org/0000-0002-4244-5417>

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