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)

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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. The inclusion and follow-up in this register will grow 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.

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.
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 shared 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://cgl.lemnov.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% of the 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.
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.

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

| Number of patients enrolled | Number | 95% CI |
|-----------------------------|--------|--------|
| 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

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*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 spondylarthritides, one case of SAPHO syndrome (an acronym for synovitis, acne, pustulosis, hyperostosis, osteitis), three cases of Still’s disease, two cases of idiopathic periarteritis, one case of unclassified autoimmune inflammatory 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.

### 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 Staphylococcus epidermidis                      |
| 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 Campylobacter jejuni |
| Behçet’s                         | 31  | M   | Baricitinib            | 2                                         | None                        | Toxic pancytopenia                                          |
| Behçet’s                         | 47  | F   | Tocilizumab            | 1                                         | CS 15 mg/day+MTX+CMQ         | Malignant otitis with Pseudomonas aeruginosa                |
| Sjögren’s syndrome+anti-Jo1      | 27  | F   | Belimumab+rituximab    | 2                                         | CS 7.5 mg/day+MTX            | Tenosynovitis with Malmoense mycobacteria                   |
| 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 events (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 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) 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 (obinutuzumab 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. 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.

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, plasmocytes, etc), and the initial data in literature regarding JAK/STAT inhibitors in systemic lupus erythematosus and in myopathies or daratumumab in systemic lupus erythematosus. 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 depletion 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.

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Patient and public involvement statement All data are collected solely from the hospital medical record, with no additional information requested directly from patients. All patients included in the TATA registry were informed in writing about the objectives of the research and their rights regarding their personal data and gave their consent prior to inclusion.

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