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Diagnosis and treatment of *Tropheryma whipplei* infection in patients with inflammatory rheumatic disease: Data from the French Tw-IRD registry

Damien Caillet Portillo [a,*], Xavier Puéchal [b,c,1], Maëva Masson [a], Marie Kostine [d], Alexia Michaut [e], André Ramon [f], Daniel Wendling [g,2], Nathalie Costedoat-Chalumeau [b,c], Pascal Richette [h], Hubert Marotte [i], Justine Vix-Portet [j], Jean-Jacques Dubost [k], Sébastien Ottaviani [l], Gaël Mouterde [m], Anne Grasland [n], Aline Frazier [h], Vincent Germain [o], Fabienne Coury [p], Anne Tournadre [k], Martin Soubrier [k], Laurent Cavalie [q], Pauline Brevet [r], Laurent Zabraniecki [a], Bénédicte Jamard [a], Guillaume Couture [a], Laurent Arnaud [s], Christophe Richez [d], Yannick Degboé [a], Adeline Ruyssen-witrand [a,t], Arnaud Constantin [a,*]

[a] *Pierre-Paul Riquet University Hospital, Toulouse & Toulouse III University - Paul Sabatier, Rheumatology, Toulouse, France*
[b] *National Referral Centre for Rare Systemic Autoimmune Diseases, Department of Internal Medicine, Hôpital Cochin, AP-HP Centre, Paris, France*
[c] *Université Paris Cité, Paris, France*
[d] *Department of Rheumatology, National Reference Center for Systemic Autoimmune Rare Diseases RESO, Bordeaux University Hospital, Bordeaux, France*
[e] *Hospital Centre, Loire Vendée Ocean, Rheumatology, La Roche-sur-Yon, France*
[f] *Le Bocage Hospital, University Hospital of Dijon, Rheumatology, Dijon, France*
[g] *CHU de Besançon, Service de Rhumatologie, Université de Franche-Comté, Besançon, France*
[h] *Hôpital Lariboisière Hospital, AP-HP, Paris, Rheumatology, Paris, France*
[i] *Université Jean Monnet Saint-Étienne, CHU Saint-Étienne, Service de Rhumatologie, Mines Saint-Etienne, INSERM, SAINBIOSE U1059, F-42023 Saint-Etienne, France*
[j] *University Hospital of Poitiers, Rheumatology, Poitiers, France*
[k] *CHU Clermont-Ferrand, Université Clermont Auvergne, INRAe, Department of Rheumatology, Clermont Ferrand, France*
[l] *Bichat - Claude-Bernard Hospital, AP-HP, Paris, Rheumatology, Paris, France*
[m] *Rheumatology Department, CHU Montpellier & IDESP, Montpellier University, Montpellier, France*
[n] *Louis-Mourier Hospital, AP-HP, Université Paris Cité, Rheumatology, Colombes, France*
[o] *Pau Hospital, Rheumatology, Pau, France*
[p] *University of Lyon, University Lyon 1, Department of Rheumatology, Lyon Sud Hospital, Hospices Civils de Lyon, Lyon Immunopathology Federation (LIFe), INSERM UMR 1033, Lyon, France*
[q] *Bacteriology and Hygiene Laboratory, Federal Institute of Biology (IFB), Purpan Hospital, Toulouse & IRSD, INSERM, INRAE, ENVT Toulouse III University - Paul Sabatier, Toulouse, France*
[r] *Department of Rheumatology and CIC-CRB 1404, Inserm 1234, Rouen University, Rouen, France*
[s] *Hautepierre Hospital, University Hospital of Strasbourg, Rheumatology, Strasbourg, France*
[t] *Centre d'Investigation Clinique de Toulouse CIC1436, Inserm, Team PEPSS "Pharmacologie En Population Cohortes et Biobanques", Toulouse, France*

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SUMMARY

Objectives: *Tropheryma whipplei* infection can manifest as inflammatory joint symptoms, which can lead to misdiagnosis of inflammatory rheumatic disease and the use of disease-modifying antirheumatic drugs. We investigated the impact of diagnosis and treatment of *Tropheryma whipplei* infection in patients with inflammatory rheumatic disease.
Methods: We initiated a registry including patients with disease-modifying antirheumatic drugs-treated inflammatory rheumatic disease who were subsequently diagnosed with *Tropheryma whipplei* infection. We

* Correspondence to: Pierre-Paul Riquet University Hospital, Toulouse & Toulouse III University - Paul Sabatier, Rheumatology, Toulouse, France.
E-mail addresses: cailletportillo@gmail.com (D. Caillet Portillo), constantin.a@chu-toulouse.fr (A. Constantin).
[1] ORCID: 0000-0003-3573-9203.
[2] ORCID: 0000-0002-4687-5780.

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collected clinical, biological, treatment data of the inflammatory rheumatic disease, of *Tropheryma whipplei* infection, and impact of antibiotics on the evolution of inflammatory rheumatic disease.
Results: Among 73 inflammatory rheumatic disease patients, disease-modifying antirheumatic drugs initiation triggered extra-articular manifestations in 27% and resulted in stabilisation (51%), worsening (34%), or improvement (15%) of inflammatory rheumatic disease. At the diagnosis of *Tropheryma whipplei* infection, all patients had rheumatological symptoms (mean age 58 years, median inflammatory rheumatic disease duration 79 months), 84% had extra-rheumatological manifestations, 93% had elevated C-reactive protein, and 86% had hypoalbuminemia. Treatment of *Tropheryma whipplei* infection consisted mainly of doxycycline plus hydroxychloroquine, leading to remission of *Tropheryma whipplei* infection in 79% of cases. Antibiotic treatment of *Tropheryma whipplei* infection was associated with remission of inflammatory rheumatic disease in 93% of cases and enabled disease-modifying antirheumatic drugs and glucocorticoid discontinuation in most cases.
Conclusions: Tropheryma whipplei infection should be considered in inflammatory rheumatic disease patients with extra-articular manifestations, elevated C-reactive protein, and/or hypoalbuminemia before disease-modifying antirheumatic drugs initiation or in inflammatory rheumatic disease patients with an inadequate response to one or more disease-modifying antirheumatic drugs. Positive results of screening and diagnostic tests for *Tropheryma whipplei* infection involve antibiotic treatment, which is associated with complete recovery of *Tropheryma whipplei* infection and rapid remission of inflammatory rheumatic disease, allowing disease-modifying antirheumatic drugs and glucocorticoid discontinuation.

Introduction

Whipple's disease is a rare infectious disease, with an estimated prevalence of 1 to 10 cases per million and mainly affecting white males over the age of 50 years.[1–4] The disease is characterised by arthralgia, weight loss, abdominal pain, and diarrhoea[1–3] and is caused by chronic infection with Gram-positive bacillus *Tropheryma whipplei* (Tw). Tw is ubiquitously present in the environment and transmitted by the faecal-oral or oral-oral route from a solely human pool.[5]

Apart from Whipple's disease, the spectrum of Tw infection includes chronic localised infections, acute infections, and the possibility of an asymptomatic carrier state.[3] Tw infections have the distinctive characteristic of starting with isolated rheumatological signs in almost three-quarters of cases,[6–8] which can precede diagnosis by 5 to 10 years.[6,7] There can also be a second phase of digestive symptoms, which may be associated with systemic complaints or other signs of organ involvement.[2]

Rheumatological symptoms most often begin with peripheral joint involvement, with intermittent and migratory oligoarthritis or polyarthritis that affects the large joints.[6,7] Signs of axial involvement, such as inflammatory back pain,[6,9,10] as well as tenosynovitis and bursitis,[11] may be associated with peripheral joint involvement that, when chronic, may lead to a misdiagnosis of rheumatoid arthritis (RA), spondyloarthritis (SpA), or psoriatic arthritis (PsA).[9,10] The activity of these chronic inflammatory rheumatic diseases (IRDs) may lead to treatment with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biological disease-modifying antirheumatic drugs (bDMARDs), or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs),[9,10,12] which often have no effect on rheumatological symptoms[12] and may reveal or exacerbate digestive signs,[13] systemic manifestations, or the involvement of other organs, resulting in cardiological, pneumological, or neurological symptoms that may eventually lead to the patient's death.[14–16]

Based on these findings, we hypothesised that treatment of Tw infection subsequently diagnosed in patients with misdiagnosed IRDs could have a favourable impact on rheumatological and extra-rheumatological symptoms attributed to IRDs, allowing treatment with DMARDs to be discontinued. To validate this hypothesis, we initiated a French national registry including patients with IRD treated with DMARDs who were subsequently diagnosed with Tw infection (Tw-IRD registry). Our objectives were to describe the demographic, clinical, and therapeutic characteristics of IRDs before the diagnosis of Tw infection, the diagnostic and therapeutic modalities of Tw infection, and the impact of treating Tw infection on the evolution of IRDs and their treatment.

Patients and methods

Study design

As part of an observational, retrospective, multicentre study, we established a French registry of Tw infections diagnosed in patients with chronic IRDs that led to treatment with a DMARD. These cases came from French hospitals and were identified through a call for observations via the Club Rhumatismes et Inflammations (CRI) (http://www.cri-net.com/recherche/etudes-interactives-du-cri/showEtude.asp?ID=548E438A).

Inclusion criteria

Patients included in the Tw-IRD registry had to be over 18 years of age with a chronic IRD diagnosed by the referring clinician, undergone justified treatment with ≥1 csDMARD, bDMARD, and/or tsDMARD, and been subsequently diagnosed with Tw infection by the referring clinician based on specific polymerase chain reaction (PCR), histology with periodic acid-Schiff (PAS) staining, and/or immunohistochemistry.[2]

Data collection methods

Data were collected using a standardised case report form, which can be downloaded from the Club Rhumatismes et Inflammations website (http://www.cri-net.com/recherche/etudes-interactives-du-cri/showEtude.asp?ID=548E438A). The form was completed by the patient's referring clinician based on their medical record. Data collected for each patient included demographic, clinical, and therapeutic characteristics of IRD prior to diagnosis of Tw infection; clinical and biological characteristics at the time of Tw infection diagnosis; diagnostic, therapeutic, and evolutionary modalities of the Tw infection; and the impact of Tw infection treatment on the progression of the IRD and its treatment.

Regulatory considerations

This non-interventional study was registered and approved by the Research and Innovation Department of Toulouse University Hospital (number: RnIPH 2020-136). The study was conducted in

accordance with reference methodology MR-004 of the National Commission for Information Technology and Civil Liberties (CNIL) governing the processing of personal data (number 2206723 v 0). In accordance with French ethics law, patients were informed that their coded data would be used for the study.

Statistical analysis

Data processing was performed in Excel 2019®. The normality of variable sequences was analysed by the Shapiro-Wilk test. Quantitative variables with a normal distribution were described as their mean ± standard deviation (SD), the others as their median and interquartile range (IQR). Categorical variables were described as numbers and percentages.

Results

As part of the Tw-IRD registry, we collected 76 observations from 16 French hospitals between September 2019 and February 2021. Three observations that did not meet the inclusion criteria were discarded: two patients with chronic IRDs that did not have justification for treatment with DMARDs and one patient whose diagnosis with Tw infection was not based on PCR, histology with PAS staining, and/or immunohistochemistry.[2] The data collected from the 73 observations meeting the inclusion criteria were used in the analysis.

Characteristics of inflammatory rheumatic diseases before diagnosis of Tropheryma whipplei infection

Of the 73 included patients, 57 (78.1%) were men. The mean ± SD age at the time of IRD diagnosis was 48.6 ± 10.9 years (Table 1). A diagnosis of RA was made by the referring clinicians in 31 (42.5%) of the 73 patients, 51.6% of whom (16/31) met the ACR 2010 criteria,[17] 13.3% (4/30) were rheumatoid factor (RF) positive, 9.7% (3/31) were anti-citrullinated protein antibody (ACPA) positive, and 54.8% (17/31) had joint erosion (Table 1). A diagnosis of SpA was made by the referring clinicians in 14 (19.2%) of the 73 cases, 57.1% (8/14) of which met the ASAS criteria,[18] 28.6% (4/14) had radiographic sacroiliitis, 21.4% (3/14) had magnetic sacroiliitis, and 21.4% (3/14) were HLA-B27 positive (Table 1). A diagnosis of PsA was made by the referring clinicians in 6 (8.2%) of the 73 cases, 66.7% (4/6) of which met the CASPAR classification criteria[19] and 50.0% (3/6) had joint erosion (Table 1).

The referring clinicians diagnosed another type of IRD in 22 (30.1%) of the 73 patients, including 6 with palindromic rheumatism, 4 with connective tissue disease (2 systemic lupus, 2 Sjögren's), 2 autoinflammatory diseases, 2 cases of polymyalgia rheumatica, 1 case of Behçet's disease, 1 case of sarcoidosis, and 6 unclassified IRDs (Table 1).

Table 1
Demographic and clinical characteristics of inflammatory rheumatic diseases before diagnosis of *Tropheryma whipplei* infection.

Mean age (± SD) at diagnosis of IRD, years	48.6 (± 10.9)
Gender ratio (male/female)	3.6 (57/16)
Median (IQR) duration of IRD, months	79 (36;140)
Type of IRD	**% (n/N)**
– Rheumatoid arthritis	42.5 (31/73)
o ACR2010 criteria	51.6 (16/31)
o RF positive	13.3 (4/30)
o ACPA positive	9.7 (3/31)
o RF and ACPA positive	6.7 (2/30)
o Presence of joint erosion	54.8 (17/31)
– Spondyloarthritis	19.2 (14/73)
o ASAS criteria	57.1 (8/14)
o Radiographic sacroiliitis	28.6 (4/14)
o Magnetic sacroiliitis	21.4 (3/14)
o Presence of HLA-B27	21.4 (3/14)
– Psoriatic arthritis	8.2 (6/73)
o CASPAR criteria	66.7 (4/6)
o Presence of joint erosion	50.0 (3/6)
– Other type of IRD	30.1 (22/73)
o Palindromic rheumatism	8.2 (6/73)
o Connective tissue disease	5.5 (4/73)
o Auto-inflammatory disease	2.7 (2/73)
o Polymyalgia rheumatica	2.7 (2/73)
o Behçet's disease	1.4 (1/73)
o Sarcoidosis	1.4 (1/73)
o Unclassified IRD	8.2 (6/73)

n = observed class size, N = total class size, IRD = inflammatory rheumatic diseases, ACR = American College of Rheumatology, RF = rheumatoid factor, ACPA = anti-citrullinated protein antibody, ASAS = Assessment in SpondyloArthritis International Society, CASPAR = Classification of Psoriatic Arthritis, SD = standard deviation, IQR = interquartile range.

Table 2
Therapeutic modalities of inflammatory rheumatic diseases before diagnosis of *Tropheryma whipplei* infection.

	% (n/N)
Exposure to DMARDs prior to diagnosis of Tw infection	
Exposure to DMARDs	100 (73/73)
Exposure to csDMARDs	94.5 (69/73)
– 1 csDMARD	43.8 (32/73)
– 2 csDMARDs	27.4 (20/73)
– ≥3 csDMARDs	23.3 (17/73)
Exposure to bDMARDs	63.0 (46/73)
– 1 bDMARD	13.7 (10/73)
– 2 bDMARDs	16.4 (12/73)
– ≥3 bDMARDs	32.9 (24/73)
Exposure to tsDMARDs	5.5 (4/73)
– 1 tsDMARD	4.1 (3/73)
– 2 tsDMARDs	1.4 (1/73)
Treatment in progress at the time of diagnosis with Tw infection	
Treatment with DMARDs	95.9 (70/73)
Treatment with csDMARD	71.2 (52/73)
– 1 csDMARD	67.1 (49/73)
– 2 csDMARDs	4.1 (3/73)
Treatment with bDMARDs	54.8 (40/73)
– Monotherapy	42.5 (17/40)
– Combination with 1 csDMARD	57.5 (23/40)
Treatment with tsDMARD	2.7 (2/73)
Treatment with glucocorticoids	61.6 (45/73)
– Daily dose > 5 mg/d (eq prednisone)	73.3 (33/45)
Treatment with NSAIDs	27.4 (20/73)
Efficacy and tolerability of IRD treatments prior to diagnosis of Tw infection	
Treatment efficacy	
– Improvement	15.1 (11/73)
– Stabilisation	50.7 (37/73)
– Worsening	34.3 (25/73)
Treatment tolerability	
– Occurrence of extra-articular symptoms	27.4 (20/73)
– Type of extra-articular symptoms	
o Systemic symptoms	40.0 (8/20)
o Cardiovascular symptoms	25.0 (5/20)
o Neurological symptoms	25.0 (5/20)
o Digestive symptoms	20.0 (4/20)
o Pneumological symptoms	15.0 (3/20)
o Ophthalmological symptoms	5.0 (1/20)
o Spondylodiscitis	5.0 (1/20)

n = observed number per class, N = total number per class, Tw = Tropheryma whipplei, IRD = inflammatory rheumatic diseases, DMARDs = disease-modifying antirheumatic drugs, csDMARDs = conventional synthetic DMARDs, bDMARDs = biologic DMARDs, tsDMARDs = targeted synthetic DMARDs, eq = equivalent, NSAID = non-steroidal anti-inflammatory drug, IQR = interquartile range.

Therapeutic modalities of inflammatory rheumatic diseases before diagnosis of Tropheryma whipplei infection

In line with the inclusion criteria, 100% (73/73) of patients were treated with a DMARD prior to Tw diagnosis, including ≥1 csDMARD in 94.5% (69/73) of cases, bDMARD in 63.0% (46/73) of cases, or tsDMARD in 5.5% (4/73) of cases (Table 2). At the time of Tw

diagnosis, 70 (95.9%) of the 73 patients were being treated with DMARDs, including 71.2% (52/73) with csDMARDs [69.2% (36/52) with methotrexate, 15.4% (8/52) with leflunomide, 11.5% (6/52) with hydroxychloroquine, 5.8% (3/52) with azathioprine, and 3.8% (2/52) with sulfasalazine], 54.8% (40/73) with bDMARDs [60.0% (24/40) with TNF inhibitor, 15.0% (6/40) with IL-1R antagonist, 7.5% (3/40) with anti-IL-6R, 7.5% (3/40) with anti-CD20, 5.0% (2/40) with anti-IL-17%, and 5.0% (2/40) with CTLA4-Ig], and 2.7% (2/73) with a tsDMARD (tofacitinib). In addition, 61.6% (45/73) of all patients in the sample were being treated with glucocorticoids and 27.4% (20/73) with non-steroidal anti-inflammatory drugs (NSAIDs) (Table 2).

When assessing the efficacy of DMARDs used to treat chronic IRD prior to diagnosis with Tw infection, referring clinicians reported improvement of the IRD in 15.1% (11/73) of cases, stabilisation in 50.7% (37/73), and worsening in 34.3% (27/73) (Table 2). Referring clinicians reported the development of extra-articular symptoms in 20 (27.4%) of the 73 patients, with systemic symptoms in 40.0% (8/20) of these cases, cardiovascular symptoms in 25.0% (5/20), neurological symptoms in 25.0% (5/20), digestive symptoms in 20.0% (4/20), pneumological symptoms in 15.0% (3/20), ophthalmological symptoms in 5.0% (1/20), and spondylodiscitis in 5.0% (1/20) (Table 2).

Clinical and biological characteristics of Tropheryma whipplei infection

The mean ± SD age at diagnosis of Tw infection was 58.4 ± 10.1 years. The median (IQR) duration of IRD was 79 (36; 140) months (Table 3).

At the time of diagnosis of Tw infection, rheumatological symptoms were present in 100% (73/73) of cases, with peripheral joint involvement in 100% (73/73) of cases [98.6% (72/73) had arthralgia and 86.3% (63/73) had arthritis]. The topography and type of involvement were polyarticular in 56.5% (39/69) of cases, oligoarticular in 42.0% (29/69), and monoarticular in 1.5% (1/69), with large joints affected in 90.3% (65/72) of cases and small joints in 62.5% (45/72). Evidence of axial involvement was reported in 32.9% (24/73) of patients, with inflammatory back pain in 100% (24/24) of these cases. Symptoms of enthesis involvement were reported in 11.0% (8/73) of patients, 75.0% (6/8) including heel pain (Table 3).

At the time of diagnosis of Tw infection, 83.6% (61/73) of patients had extra-rheumatological symptoms. Digestive symptoms were present in 65.8% (48/73) of cases, with weight loss in 53.4% (39/73), diarrhoea in 41.1% (30/73), and abdominal pain in 27.4% (20/73) of all cases. Systemic symptoms were present in 60.3% (44/73) of patients, with asthenia in 54.8% (40/73) and fever in 38.4% (28/73). Other clinical manifestations included superficial adenopathy (28.8%, 21/73), cardiovascular symptoms (19.2%, 14/73), pneumological symptoms (15.1%, 11/73), neurological symptoms (15.1%, 11/73), dermatological symptoms (15.1%, 11/73), muscular symptoms (6.9%, 5/73), and ophthalmological symptoms (5.5%, 4/73) (Table 3).

At the time of diagnosis with Tw infection, the median (IQR) CRP (C-reactive protein) level was 56.2 (28.5; 86.5) mg/L, with CRP ≥5 mg/L in 92.5% (62/67) of cases, > 50 mg/L in 59.7% (40/67) of cases, and > 100 mg/L in 19.4% (13/67) of cases. The mean ± SD albumin level was 32.8 ± 7.6 g/L, with albumin < 40 g/L in 85.7% (48/56) of cases, < 35 g/L in 57.1% (32/56) of cases, and < 30 g/L in 39.3% (22/56) of cases. Anaemia (defined as haemoglobin < 12 g/dL in women or < 13 g/dL in men) was observed in 66.7% (40/60) of patients, and 61.1% (33/54) had neutrophil leucocytosis (defined as neutrophil count ≥7.5 G/L) (Table 3).

Diagnostic procedures for Tropheryma whipplei infection

Screening for Tw infection involved specific PCR of saliva samples in 66 (90.4%) of the 73 patients and faecal samples in 63 (86.3%), which was positive in 80.3% (53/66) and 90.5% (57/63) of cases, respectively (Table 4). Diagnostic confirmation of Tw infection was mostly based on the results of duodenal biopsies (PCR, histology with PAS staining, and immunohistochemistry), which were performed in 95.9% (70/73) of cases. Duodenal PCR was positive in 87.1% (61/70) of evaluations, histology with PAS staining in 37.8% (25/66), and immunohistochemistry in 43.8% (7/16) (Table 4).

Diagnosis was also based on the results of other biological samples in 86.3% (63/73) of patients. PCR was positive in blood in 33.3% (15/45) of tested cases, cerebrospinal fluid in 33.3% (14/42) of tested cases, synovial fluid in 86.4% (19/22) of tested cases, and pleural fluid in 100% (1/1) of tested cases. Tissue PCRs were positive in skin biopsies in 63.6% (7/11) of tested cases, heart valve biopsies in 100% (2/2) of tested cases, lymph node biopsies in 100% (2/2) of tested cases, and disco-vertebral biopsies in 100% (1/1) of tested cases (Table 4).

Table 3
Clinical and biological characteristics of *Tropheryma whipplei* infection.

Mean age (± SD) at diagnosis of Tw infection, years	58.4 (± 10.1)
Median (IQR) duration of IRD, months	79 (36;140)
Clinical characteristics	**% (n/N)**
Rheumatological symptoms	100.0 (73/73)
– Peripheral joint involvement	100.0 (73/73)
o Arthralgia	98.6 (72/73)
o Arthritis	86.3 (63/73)
o Topography and type of involvement	
▪ Polyarticular involvement	56.5 (39/69)
▪ Oligoarticular involvement	42.0 (29/69)
▪ Monoarticular involvement	1.5 (1/69)
▪ Large joint involvement	90.3 (65/72)
▪ Small joint involvement	62.5 (45/72)
– Axial involvement	32.9 (24/73)
– Entheseal involvement	11.0 (8/73)
Digestive symptoms	65.8 (48/73)
– Weight loss	53.4 (39/73)
– Diarrhoeal	41.1 (30/73)
– Abdominal pain	27.4 (20/73)
Systemic symptoms	60.3 (44/73)
– Asthenia	54.8 (40/73)
– Fever	38.4 (28/73)
Superficial adenopathy	28.8 (21/73)
Cardiovascular symptoms	19.2 (14/73)
Pneumological symptoms	15.1 (11/73)
Neurological symptoms	15.1 (11/73)
Dermatological symptoms	15.1 (11/73)
Muscular symptoms	6.9 (5/73)
Ophthalmological symptoms	5.5 (4/73)
Biological characteristics	
CRP, median (IQR), mg/L	56.2 (28.5;86.5)
– CRP ≥5 mg/L	92.5 (62/67)
– CRP > 50 mg/L	59.7 (40/67)
– CRP > 100 mg/L	19.4 (13/67)
Albumin, mean (± SD), g/L	32.8 (± 7.6)
– Hypoalbuminemia (< 40 g/L)	85.7 (48/56)
– Moderate hypoalbuminemia (< 35 g/L)	57.1 (32/56)
– Severe hypoalbuminemia (< 30 g/L)	39.3 (22/56)
Haemoglobin, g/dL	
Mean (± SD) female	11.0 (± 1.7)
Mean (± SD) male	12.1 (± 2.1)
– Anaemia*	66.7 (40/60)
Polynuclear neutrophils, mean (± SD), G/L	8.6 (± 3.5)
– Neutrophil leucocytosis (≥7.5 G/L)	61.1 (33/54)

n = observed number of patients per class, N = total number of patients per class, Tw = *Tropheryma whipplei*, IRD = inflammatory rheumatic disease, CRP = C-reactive protein, SD = standard deviation, IQR = interquartile range.
* Anaemia was defined as haemoglobin < 12 g/dL in women or < 13 g/dL in men.

Therapeutic modalities and evolution of Tropheryma whipplei infection

The median (IQR) follow-up duration after the start of treatment for Tw infection was 21.5 (10; 36) months. Data regarding the evolution of Tw infection were available for only 72 patients, with 1 patient dropping out after diagnosis (Table 5).

Table 4
Diagnostic procedures for *Tropheryma whipplei* infection.

	Examinations performed % (n/N)	Positive results % (n/N)
Screening for Tw infection		
Saliva PCR	90.4 (66/73)	80.3 (53/66)
Faecal PCR	86.3 (63/73)	90.5 (57/63)
Diagnostic confirmation of Tw infection		
Analysis of duodenal biopsies	95.9 (70/73)	
- PCR	100 (70/70)	87.1 (61/70)
- Histology with PAS staining	85.7 (66/70)	37.8 (25/66)
- Immunohistochemistry	22.9 (16/70)	43.8 (7/16)
Analysis of other biological samples	86.3 (63/73)	
Blood PCR	61.6 (45/73)	33.3 (15/45)
Cerebrospinal fluid PCR	57.5 (42/73)	33.3 (14/42)
Joint fluid PCR	30.1 (22/73)	86.4 (19/22)
Skin biopsy PCR	15.1 (11/73)	63.6 (7/11)
Heart valve biopsy PCR	2.7 (2/73)	100.0 (2/2)
Lymph node biopsy PCR	2.7 (2/73)	100.0 (2/2)
Disco-vertebral biopsy PCR	1.4 (1/73)	100.0 (1/1)
Pleural fluid PCR	1.4 (1/73)	100.0 (1/1)

n = observed number per class, N = total number per class, Tw = *Tropheryma whipplei*, PCR = polymerase chain reaction, PAS = periodic acid shift.

Table 5
Therapeutic modalities and evolution of *Tropheryma whipplei* infection.

Median (IQR) duration of follow-up after initiation of treatment for Tw infection, months	21.5 (10;36)
Treatment for Tw infection	**% (n/N)**
Hydroxychloroquine	95.9 (70/73)
Doxycycline	94.5 (69/73)
Ceftriaxone	17.8 (13/73)
Trimethoprim/sulfamethoxazole	13.7 (10/73)
Sulfadiazine	11.0 (8/73)
Penicillin G	2.7 (2/73)
Evolution of Tw infection*	**% (n/N)**
Remission	79.2 (57/72)
Improvement	18.1 (13/72)
IRIS	5.6 (4/72)
Death	2.8 (2/72)

n = observed class size, N = total class size, Tw = Tropheryma whipplei, IRIS = immune reconstitution inflammatory syndrome.
* Data regarding the progression of TW infection were available for 72 patients (1 patient dropped out after diagnosis of Tw infection).

The treatment for Tw infection involved hydroxychloroquine in 95.9% (70/73) of cases, with a median (IQR) duration of treatment of 16 (12;22.5) months; doxycycline in 94.5% (69/73) of cases, with a median (IQR) duration of treatment of 20 (14.25; 29.25) months; ceftriaxone in 17.8% (13/73) of cases; combination of trimethoprim and sulfamethoxazole in 13.7% (10/73) of cases; sulfadiazine in 11.0% (8/73) of cases; and penicillin G in 2.7% (2/73) of cases (Table 5).

The evolution of Tw infection under treatment led to remission in 79.2% (57/72) of cases, improvement in 18.1% (13/72), and immune reconstitution inflammatory syndrome (IRIS) in 5.6% (4/72). The outcome of Tw infection was fatal in 2 (2.8%) of the 72 cases: one case of multi-organ failure occurring less than 1 month after the start of antibiotic treatment in a patient with Tw spondylodiscitis, and one case of haemorrhagic stroke occurring in a patient in remission 4 months after the start of antibiotic treatment (Table 5).

Impact of treatment of Tropheryma whipplei infection on the evolution of inflammatory rheumatic disease and its treatment

Data regarding the evolution of IRD were available for 72 patients (Table 6). After the start of treatment for Tw infection, 67 (93.1%) of the patients were considered to be in remission for the IRD, with a median (IQR) time to remission of 2 (1; 4.25) months; 4 (5.6%) were considered to be stable; and 1 (1.4%) patient (with Tw spondylodiscitis) had worsened to multi-organ failure.

Table 6
Impact of treatment of *Tropheryma whipplei* infection on the evolution of inflammatory rheumatic disease and its treatment.

Median (IQR) duration of follow-up after initiation of treatment for Tw infection, months	21.5 (10;36)
*Evolution of the IRD**	**% (n/N)**
Remission	93.1 (67/72)
• Median (IQR) for achieving remission, months	2 (1;4.25)
Stabilisation	5.6 (4/72)
Worsening	1.4 (1/72)
Adaptation of IRD treatment	**% (n/N)**
DMARDs	
• Stopped	94.2 (65/69)
• Reduced dosage**	1.5 (1/69)
• Increased dosage***	4.4 (3/69)
Glucocorticoids	
• Stopped	65.1 (29/44)
• Hydrocortisone replacement	11.4 (5/44)
• Reduced dosage	20.5 (9/44)
• Unchanged	2.3 (1/44)
NSAIDs	
• Stopped	90.0 (18/20)
• Reduced dosage	10.0 (2/20)

n = observed class size, N = total class size, IQR = interquartile range, Tw = *Tropheryma whipplei*, IRD = inflammatory rheumatic diseases, NSAIDs = non-steroidal anti-inflammatory drugs.
* IRD progression data available for 72 patients (1 patient dropped out after diagnosis with Tw infection).
** Continuation of methotrexate and discontinuation of bDMARD,
*** 3 patients on hydroxychloroquine.

IRD treatments were decreased or discontinued in the majority of patients after the start of treatment for Tw infection. DMARDs were stopped in 94.2% (65/69), reduced in 1.4% (1/69), and increased (initial hydroxychloroquine dosage in order to treat Tw infection) in 4.4% (3/69). Glucocorticoids were stopped in 65.9% (29/44) of patients taking them, switched for hydrocortisone in 11.4% (5/44) of the patients, reduced in 20.5% (9/44), and unchanged in 2.3% (1/44). NSAIDs were stopped in 90.0% (18/20) and reduced in 10.0% (2/20) of the patients taking them.

Discussion

Of the 73 IRD patients from the Tw-IRD registry included in this study, most had inadequate responses to DMARDs, which frequently resulted in the occurrence of extra-articular manifestations. The diagnosis of Whipple's disease was made after an IRD duration of 7 years, with rheumatological symptoms in all patients and most of the cases experiencing extra-rheumatological manifestations, persistent elevation of CRP, or hypoalbuminemia. In accordance with previous observational studies involving patients with Whipple's disease, several types of IRDs were reported in our registry, but mainly RA, SpA, and PsA, reflecting the type and topography of rheumatological symptoms affecting the peripheral joints, spine, or entheseal territory.[7,9,10] Our registry is the first to systematically assess the classification criteria for RA, SpA, and PsA in patients subsequently diagnosed with Tw infection. Only half of the patients met the ACR/EULAR 2010 criteria for RA,[17] ASAS criteria for SpA,[18,20] or CASPAR criteria for PsA,[19] with an abnormally low frequency of RF or ACPA positivity for RA[6,7] and abnormally low frequency of radiographic or magnetic sacroiliitis or HLA-B27 for SpA.[21] Interestingly, joint erosions were observed in half of the patients diagnosed with RA or PsA.[16,22] The diversity of IRDs reported in our registry and the atypical presentation of these IRDs reflect the diversity of rheumatological symptoms observed during Whipple's disease, which may lead the referring clinician to misdiagnose IRD and inappropriately initiate DMARDs before the diagnosis of Tw infection.[9,10,23]

According to the inclusion criteria for our registry, all patients were exposed to DMARDs before diagnosis with Tw. Most of them had inadequate responses to csDMARDs and/or bDMARDs, which frequently resulted in the IRD worsening or in the occurrence of extra-articular manifestations. The harmful effect of DMARD initiation was previously reported in observational studies involving patients with Whipple's disease.[9,10,12,14,15,24] It must be considered a red flag in patients with IRDs, particularly those with atypical presentation, and it should lead the clinician to perform screening tests for Tw infection.

Patient characteristics at the time of diagnosis with Tw infection were in accordance with previous observational studies, with a predominance of middle aged males,[9,25] long IRD duration,[7,9] and preferentially affecting the peripheral joints, with polyarticular and large joint involvement.[6,7,10,26] A majority of patients had extra-rheumatological symptoms, which are comparable to those reported in other sets of patients with Tw infections.[2,9] A large majority of patients had persistent elevation of CRP, hypoalbuminemia, or anaemia, initially considered to be linked to their IRD but consistent with the biological abnormalities observed in other series of patients with Tw infection.[1,27]

In our registry, screening for Tw infection was based on saliva and faecal specific PCR,[2,3,28] with good sensitivity.[28] Although there is currently no consensus, the use of non-invasive methods, such as saliva PCR and faecal PCR, appears to be appropriate for the detection of Tw.[2,3] Diagnostic confirmation of Whipple's disease was based on analysis of duodenal biopsies in most patients, with a high sensitivity for PCR but only 38% for PAS staining. After positive screening results, the use of an invasive method, such as duodenal biopsy, with specific PCR, histological, and immunohistochemical analysis, remains central to diagnosing Whipple's disease.[2,3,29] It has to be highlighted that most of these patients do not have a diagnosis of classical Whipple disease with a positive PAS (periodic acid Schiff) staining, which should not rule out the diagnosis. The diagnostic value of *Tropheryma whipplei*-specific PCR from duodenal specimens remains inconclusive. Duodenal biopsy specimens yielded positive PCR results in 27/72 (38%) carriers in a recent study, which has also highlighted the high specificity of duodenal PCR with low C(t) values to confirm the diagnosis of Whipple's disease.[30] In suspected cases of chronic localised infection with Tw, PCR of tissue biopsies or fluid samples from affected organs appears appropriate to confirm diagnosis.[2,3] In addition, joint fluid specific PCR is positive in most cases.[24,28] If Whipple's disease is suspected in a patient with unexplained recurrent arthritis, joint fluid-specific PCR may be systematically performed, due to its high sensibility and specificity and its diagnostic value in the differential diagnosis of all kinds infectious arthritis including articular infection with *T. whipplei*.[24,27]

The majority of patients in this study were treated with a combination of doxycycline and hydroxychloroquine, which led to remission of Tw infection in most cases.[2,27] Although there is currently no consensus on the treatment options for Whipple's disease, the combination of doxycycline and hydroxychloroquine for ≥12 months, followed by doxycycline monotherapy for varying lengths of time, appears to be appropriate for treating most patients.[3,16,28]

To the best of our knowledge, this study is the first to systematically assess the impact of treating Tw infection on the evolution of IRD and its treatment. With a median follow-up of 22 months, antibiotic treatment for Tw infection was associated with rapid remission of IRD within 2 months, allowing DMARDs, glucocorticoids, and NSAIDs discontinuation in most cases. A previous observational study involving patients with Tw infection and rheumatological manifestations reported a favourable evolution of Tw infection after antibiotic treatment in two-thirds of the patients, without details on the evolution of rheumatological manifestations in patients with established IRD.[16] The rapid remission of IRD and DMARD discontinuation observed in most cases in our registry after initiation of antibiotics for Tw infection strengthen the hypothesis that the rheumatological manifestations that led the referral clinician to make a diagnosis of IRD were related to Whipple's disease.[10,16,31]

The strengths of this study involve the constitution of a national multicentre registry including patients with IRD treated with DMARDs and subsequently diagnosed with Tw infection, with strict criteria for inclusion and standardised data collection.[9,25] The limitations of this study are its observational and retrospective design, with diagnostic, therapeutic, and evolutional modalities of IRD and Tw infection based on the clinical practices of referring clinicians.

According to the data from our registry, Tw infection should be considered in a middle-aged man with unexplained seronegative arthritis of the large joints, especially if preceded by intermittent acute episodes of arthritis or with extra-articular manifestations, elevated CRP, and/or hypoalbuminemia before DMARD initiation, or in IRD patients with an inadequate response to one or more DMARDs. The positive results of screening and diagnostic tests for Tw infection involve the initiation of antibiotic treatment, which is associated with complete recovery of Tw infection and rapid remission of IRD, allowing discontinuation of DMARDs and glucocorticoids in most cases.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Club Rhumatismes et Inflammations.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2023.12.010.

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