Which patients with rheumatoid arthritis, spondyloarthritis, or juvenile idiopathic arthritis receive TNF-α antagonists in France? The CORPUS cohort study

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Abstract

Objective

Limited information is available about the characteristics of patients with active inflammatory rheumatic diseases who start TNF-α antagonist therapy. Our objective was to assess TNF-α antagonist prescription patterns in this context in France.

Methods

Between 2007 and 2009, 102 rheumatologists, internists, and pediatricians in French university hospitals and private practice prospectively recruited biologics-naïve patients with active rheumatoid arthritis (RA) (DAS28>3.2 despite methotrexate therapy), spondyloarthritis (SA) (BASDAI≥4 despite non-steroidal anti-inflammatory drug [NSAID] use), and juvenile idiopathic arthritis (JIA) (unresponsive to methotrexate). Patients were monitored prospectively for 1 year.

Results

Of the 543 RA, 287 SA, and 53 JIA patients included in the study, 382 RA, 171 SA, and 28 JIA patients had complete follow-up data available after 1 year. Among these patients, 110/382 (28.8%) with RA, 81/171 (47.4%) with SA, and 26/28 (92.9%) with JIA received at least one TNF-α antagonist dose during the 1-year follow-up. The main physician-reported reason for not starting TNF-α antagonists in patients with RA or SA was low disease activity (72% for RA and 67% for SA); absence of TNF-α antagonist therapy was due to patient refusal in only 10% and to contraindications in 6% to 7% of cases.

Conclusion

In France, TNF-α antagonists, which are fully reimbursed by the national health insurance system, were used almost routinely in JIA patients unresponsive to methotrexate and were given to about half the SA patients with BASDAI≥4 despite NSAID use and a third of RA patients with DAS28>3.2 despite methotrexate therapy.

Key words

rheumatoid arthritis, spondylarthritis, juvenile idiopathic arthritis, biologics, DMARDs, methotrexate

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Introduction

Rheumatoid arthritis (RA) and spondyloarthritis (SA), a group of diseases encompassing ankylosing spondylitis and psoriatic arthritis, are the most common inflammatory rheumatic diseases, the prevalence of each being about 0.3% in France (1-3). The prevalence of juvenile idiopathic arthritis (JIA) has not been assessed in France nationwide but was estimated at 0.01% in one region of the country (4).

These diseases may evolve as a chronic disease responsible for functional impairments that markedly affect quality of life. Therapeutic advances have been achieved in recent years, notably with the development of biologics such as TNF-α antagonists, which are used in SA refractory to non-steroidal anti-inflammatory drugs (NSAIDs) and in both RA and JIA refractory to methotrexate and other synthetic disease-modifying anti-rheumatic drugs (DMARDs). Prescription guidelines have been developed at both the national and international level for RA, SA, and JIA. Although these guidelines are similar in Europe and in the US (5-8), many countries have cost-containment policies that restrict the use of biologics to patients who meet specific disease-activity criteria and have failed synthetic DMARD therapy (8-11).

In addition to these cost-containment efforts, other factors may affect the use of biologics. Limited information is available about patients who are potential candidates for TNF-α antagonist therapy and about physicians' attitudes toward the initiation of these drugs. In a previous survey, we found that patient selection for TNF-α antagonist therapy varied considerably with the criteria used (12), but that both disease progression and a need for high-dose glucocorticoid therapy were viewed by French rheumatologists as warranting TNF-α antagonist initiation (13).

Comprehensive guidelines for TNF-α antagonist therapy were published in 2007 by the French Society for Rheumatology (SFR) (14, 15). These guidelines have no restrictions based on cost considerations: RA with objective evidence of inflammation or progressive structural damage, or dependency on glucocorticoid therapy, or progressive radiographic damage; and failure to respond adequately to methotrexate – or another agent when methotrexate is contraindicated – in the optimal tolerated dosage therapy, or SA with active disease for more than 1 month with a BASDAI ≥4 in patients with predominantly axial disease or a tender/swollen joint count ≥3, and with a physician assessment of disease activity of ≥4/10, failure of at least three non-steroidal anti-inflammatory drugs in patients with axial disease or of disease-modifying antirheumatic drug therapy in patients with peripheral disease or JIA with an inadequate response to methotrexate therapy. Although they were not endorsed by the French drug agency (formerly AFSSAPS, now ANSM), TNF-α antagonists are reimbursed in full by the statutory health insurance system in all patients fulfilling the guideline criteria.

At the request of the French health authorities, a cohort known as CORPUS (Cohorte d'Observation Rhumatologique des pratiques et des USages) was established to assess TNF-α antagonist prescription patterns in patients with active RA, SA, or JIA.

Our goal in the current study was to evaluate the proportion of RA with DAS28>3.2 despite methotrexate therapy, SA with BASDAI≥4 despite NSAID therapy or JIA with an inadequate response to methotrexate therapy initiating a TNF-α antagonist during the first year of follow-up.

Patients and methods

The CORPUS study is a longitudinal prospective population-based cohort study of patients with RA, SA, or JIA recruited in private practices and hospitals.

Physicians and patients

All physicians authorised to prescribe biologics in France, *i.e.* rheumatologists (members of the French Society for Rheumatology [SFR]), paediatricians (members of the French-Speaking Society for Paediatric Rheumatology and Inflammatory Diseases [SOFREMIP] and/or French Society for Paediatrics [SFP]), and internists (members of the French Society for Internal Medicine

[SNFMI]) were invited to participate in this observational study between 2007 and 2009. The available data about the type of centre (primary, tertiary hospital), practice (private or public), and region of inclusion (Figure 1 shows the comparison between the French rheumatologists directory and rheumatologists participating to the corpus study) confirmed the good representativity (data not shown).

Physicians who agreed to participate were asked to recruit all patients with active disease fulfilling the following inclusion criteria: RA meeting 1987 ACR criteria with DAS28>3.2 despite methotrexate therapy (16) or SA meeting ESSG criteria with BASDAI≥4 (17) despite NSAID therapy or JIA meeting ILAR criteria with an inadequate response to methotrexate therapy (18-20). Exclusion criteria was a previous treatment by biologic agent.

Biological agents

In 2007–2009, the only biologics available in France for treating RA, SA, or JIA were TNF-α antagonists (infliximab, etanercept, and adalimumab). Patients who received at least one TNF-α antagonist dose during the 1-year study period were classified as treated with TNF-α antagonists.

Follow-up and questionnaires

Participating physicians were asked to complete a form for each patient, both at inclusion and after 1 year of prospective follow-up. The form had items on physician and practice characteristics, including the number of patients managed by the physician and receiving methotrexate and/or biologics, as well as the physician's practice patterns for these drugs. Other items collected data on the patient, including patient characteristics, co-morbidities, history of inflammatory rheumatic disease, variables needed to compute the 28-joint Disease Activity Score (DAS28) for RA (*i.e.* tender and swollen joint counts, erythrocyte sedimentation rate [ESR], and disease activity as assessed by the patient on a visual analogue scale [VAS] from 0 to 100) or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for SA (16, 17), plasma C-reactive protein (CRP) level, extra-articular manifestations (rheumatoid nodules, Sjögren's syndrome, pulmonary disorder, tendinitis, atlanto-axial dislocation, and others), radiographic findings, current and past treatments, treatment changes decided during the visit, and whether biological therapy was considered.

At study inclusion and 1 year later, each patient was asked to complete a 0–100 VAS, a health assessment questionnaire (HAQ) (21) in patients with RA or SA and Childhood HAQ (CHAQ) in those with JIA (22), and the validated French version of the quality-of-life questionnaire SF-36 (23, 24).

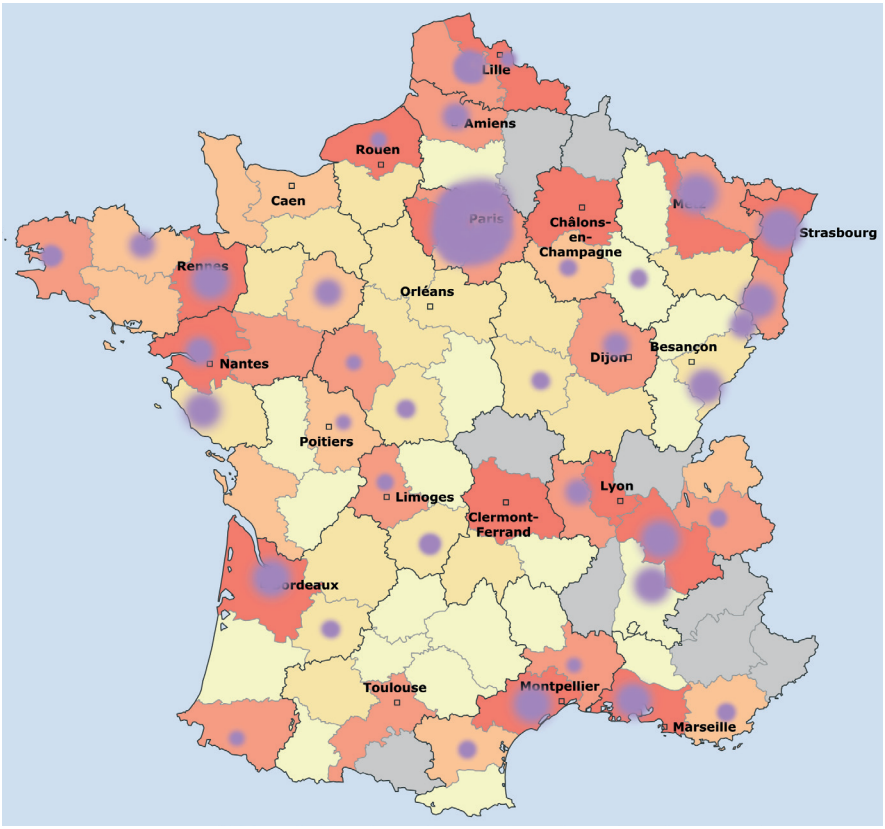

Fig. 1. Number of physicians Corpus (small circle for 0–5 and large circle for 5–20) and number of rheumatologists in France (graduation from yellow to red).

Statistics

Categorical variables were described as frequencies and continuous variables as mean±standard deviation. Associations of baseline characteristics with TNF-α antagonist initiation during the 1-year follow-up period were assessed using unconditional logistic regression. Separate associations were assessed first by univariate analysis, using the Pearson's chi-square test (or Fisher's exact test where appropriate) and the Mann-Whitney test. Variables yielding *p*-values smaller than 0.20 were entered into a multivariate logistic regression model with stepwise selection. Variables yielding *p*-values smaller than 0.05 in this model were considered independent significant predictors of TNF-α antagonist therapy initiation.

Results

Study physicians

Between 2007 and 2009, 102 physicians accepted to participate in the study, including 86 rheumatologists, 7 internists, and 9 paediatricians; 5 physicians recruited RA, SA, and JIA patients; 51 RA and SA patients; 24 only RA patients, 12 only JIA patients, and 10 only SA patients. All geographic regions of continental France were represented. In all, 883 patients were included.

Study patients

As expected, RA patients were older than SA patients (59.8 and 46.6 years,

Table I. Patients with rheumatoid arthritis, spondyloarthritis, and juvenile idiopathic arthritis with and without TNF-α antagonist therapy within 1 year after study inclusion.

	RA		SA		JIA	
	Biologics n=110	No biologics n=272	Biologics n=81	No biologics n=90	Biologics n=26	*p*-value
Demographics						
Age in y, mean (SD)	53.3 (12.03)	62.4 (12.95)	44.8 (12.53)	48.7 (13.28)	13.5 (5.84)	RA: <0.001 (4) SA: 0.050 (4)
Female, n%	84 76%	222 82%	28 35%	39 43%	18 69%	PR : 0.244 (2) SPA: 0.241 (2)
Comorbidities, n of patients, %						
Liver disease	10 9%	18 7%	3 4%	1 1%	- -	RA: 0.401 (2) SA: 0.343 (3)
Infections	20 18%	35 13%	9 11%	5 6%	3 12%	RA: 0.180 (2) SA: 0.186 (2)
Bacterial infection	11 10%	15 6%	4 5%	4 4%	3 12%	RA: 0.115 (2) SA: 1.000 (3)
Viral infection	2 2%	4 1%	2 3%	- -	1 4%	RA: 1.000 (3) SA: 0.220 (3)
Risk of infection (clinician's opinion)	1 1%	1 0%	- -	1 1%	- -	RA: 0.494 (3) SA: 1.000 (3)
Renal failure	- -	8 3%	- -	1 1%	- -	RA: 0.111 (3) SA: 1.000 (3)
Hypertension	15 14%	53 19%	10 12%	14 16%	- -	RA: 0.176 (2) SA: 0.546 (2)
Current smoker, n of patients, %	24 22%	35 13%	20 25%	16 18%	3 12%	RA: 0.028 (2) SA: 0.268 (2)
Disease activity and severity						
Patient global VAS, mean (SD)	49.9 (19.23)	55.5 (19.88)	46.8 (20.78)	59.3 (19.56)	57.5 (17.89)	RA: 0.013 (4) SA: <0.001 (4)
ESR, mm, mean (SD)	29.1 (21.15)	24.7 (18.17)	21.0 (16.80)	19.6 (19.17)	31.9 (27.86)	RA: 0.063 (5) SA: 0.247 (5)
CRP, mg/L, mean (SD)	17.7 (22.26)	16.8 (25.09)	16.6 (21.40)	12.6 (15.84)	29.8 (45.77)	RA: 0.434 (5) SA: 0.066 (5)
DAS28, mean (SD)	5.4 (1.34)	5.0 (1.22)	. (.)	. (.) .	(.)	RA: 0.013 (4)
BASDAI [0–100], mean (SD)	. (.)	. (.)	60.5 (20.51)	46.4 (19.14)	. (.)	SA: <0.001 (4)
CHAQ [0–3], mean (SD)	. (.)	. (.)	. (.)	. (.)	0.9 (0.79)	
Nodules, n%	17 15%	23 8%	- -	- -	- -	RA: 0.043 (2)
Sicca, n%	20 18%	42 15%	4 5%	4 4%	- -	RA: 0.511 (2) SA: 1.000 (3)
At least one new erosion since previous x-rays , n%	43 39%	76 28%	8 10%	19 21%	7 27%	RA: 0.033 (2) SA: 0.044 (2)
At least one prosthesis, n%	9 8%	20 7%	1 1%	1 1%	1 4%	RA: 0.789 (2) SA: 1.000 (3)
Morning stiffness in min, mean (SD)	80.2 (71.80)	49.4 (54.48)	76.2 (63.17)	39.8 (60.88)	50.5 (65.25)	RA: <0.001 (5) SA: <0.001 (5)
HAQ Score [0–3], mean (SD)	1.3 (0.66)	1.0 (0.73)	1.1 (0.69)	0.6 (0.54)	0.8 (0.56)	RA: <0.001 (4) SA: <0.001 (4)
SF36 PCS [0–100], mean (SD)	34.0 (7.42)	37.3 (8.34)	32.2 (7.53)	37.8 (8.70)	37.5 (7.54)	RA: <0.001 (4) SA: <0.001 (4)
SF36 MCS [0–100], mean (SD)	37.3 (11.20)	41.3 (11.10)	36.1 (11.28)	42.1 (11.86)	44.9 (11.78)	RA: 0.002 (4) SA: 0.001 (4)
Glucocorticoids, n%	80 73%	164 60%	17 21%	14 16%	8 31%	RA: 0.001 (4) SA: 0.357 (4)

(1) Comparison biologics/no biologics during the first year; (2) Chi-2 test; (3) Fisher exact test; (4) Student *t*-test; (5) Wilcoxon test.
RA: rheumatoid arthritis; SA: spondyloarthritis; JIA: juvenile idiopathic arthritis; VAS: visual analogue scale; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: disease activity score on 28 joints, for RA; BASDAI: Bath ankylosing spondylitis disease activity index, for SA; CHAQ: childhood health assessment questionnaire, for JIA; HAQ: health assessment questionnaire; SF36: short-form 36-item quality-of-life questionnaire; PCS: physical component summary of the SF36; MCS: mental component summary of the SF36.

respectively) and had a higher co-morbidity score. The co-morbidity score was very low in JIA patients (Table I). Disease activity as evaluated by the DAS28, BASDAI, and CHAQ scores in RA, SA, and JIA, respectively, was high in all three diagnostic groups. Disability indicators were high and quality-of-life scores displayed low values.

Of the 883 patients, 543 had RA, 287 SA, and 53 JIA, including 382 RA, 171 SA and 28 JIA patients with complete follow-up data available at 1 year. At baseline, sociodemographic characteristics, disease activity, co-morbidities, and disabilities were not significantly different between patients with and without complete 1-year data (data not shown). First prescription of biologics during the first year after study inclusion in patients with rheumatoid arthritis (RA), spondyloarthritis (SA), or juvenile idiopathic arthritis (JIA) are reported in Figure 2. Among patients with complete 1-year data, 110/382 (28.8%) with RA, 81/171 (47.4%) with SA, and 26/28 (92.9%) with JIA patients received at least one TNF-α antagonist dose during the study one-year follow-up.

Among the 543 RA patients, 100 received TNF-α antagonist therapy within 2 months after study inclusion. Among the 382 RA patients with complete 1-year data, 65 started TNF-α antagonist therapy within 2 months after inclusion, and 58 of them continued this treatment up to one year; 50 started TNF-α antagonist therapy between 2 months and 1 year after study inclusion; and 267 received no TNF-α antagonist therapy. Among the 171 SA patients with complete 1-year data, 54 started TNF-α antagonist therapy within 2 months after inclusion including 52 who were still on this treatment after 1 year; 32 started TNF-α antagonist therapy between 2 months and 1 year after inclusion; and 85 received no TNF-α antagonist therapy. Among the 28 JIA patients with complete 1-year data, 24 started TNF-α antagonist therapy within 2 months after study inclusion, including 21 still on this treatment after 1 year; 2 started TNF-α antagonist therapy between 2 months and 1 year after inclusion, and 2 received no TNF-α antagonist therapy.

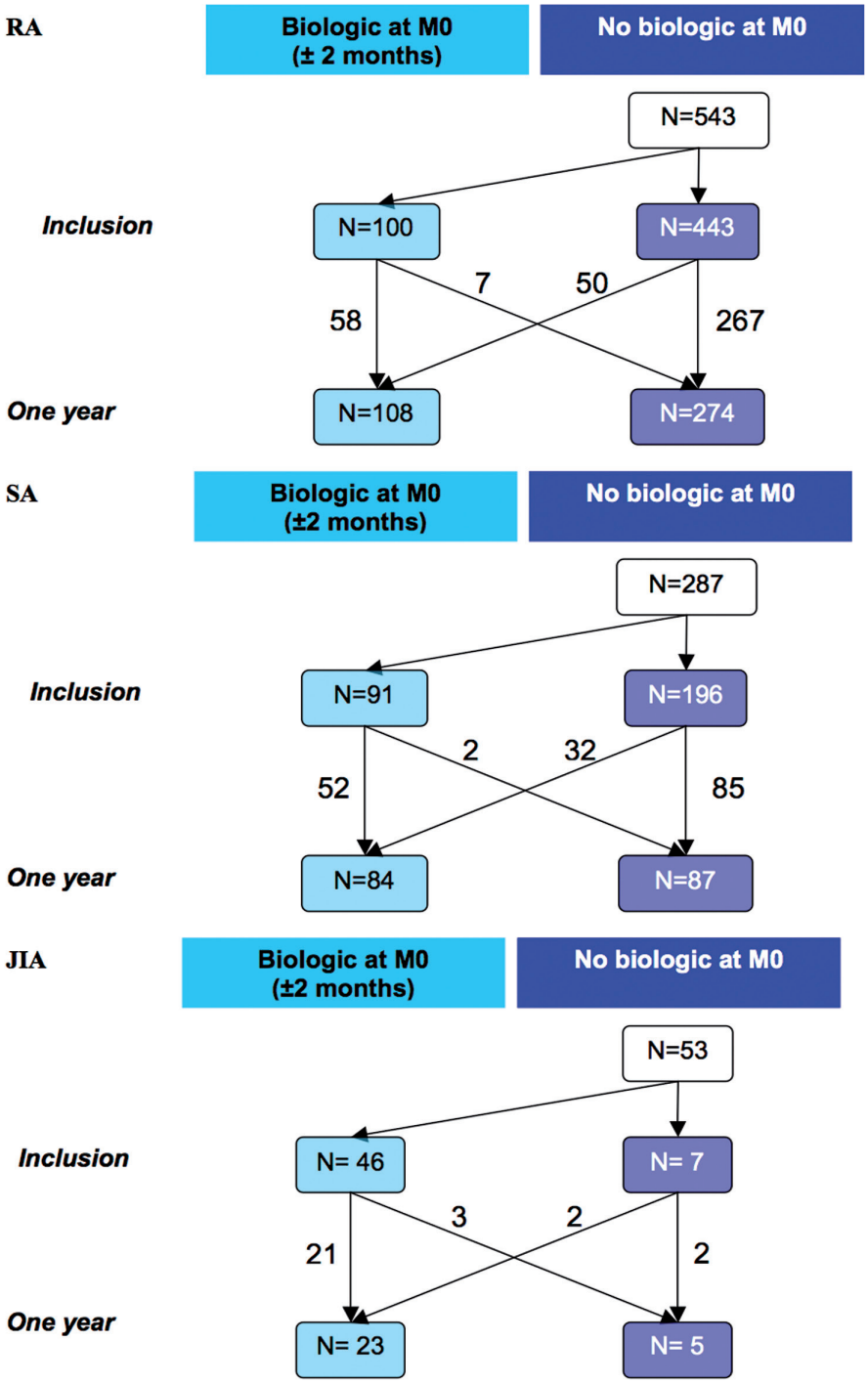

Fig. 2. First prescription of biologics during the first year after study inclusion in patients with rheumatoid arthritis (RA), spondyloarthritis (SA), or juvenile idiopathic arthritis (JIA).

Factors associated with TNF-α antagonist therapy during the first year

Baseline characteristics significantly associated with TNF-α antagonist therapy in RA patients with complete 1-year data are reported in Table I. By univariate analysis, factors associated with TNF-α antagonist therapy were younger age, smoking, glucocorticoid use, previous radiographic progression (according to physicians by x-rays comparison), higher disease activity (according to patient VAS, morning stiffness, and DAS28), worse disability (HAQ), poorer quality of life (SF36) and greater ESR. By multivariate analysis, the only factors independently associated with TNF-α antago-

Table II. Rheumatoid arthritis patients, odds ratio and 95% confidence interval for the risk of receiving biologics in RA patients, by bivariate and multivariate regression analyses.

Rheumatoid arthritis patients	Univariate				Multivariate*			
	Odds ratio	95%CI lower*	upper*	*p*-value	Odds ratio	95%CI lower*	upper*	*p*-value
Age (years)	0.95	0.93	-0.96	<0.0001	0.93	0.91	-0.95	<0.0001
Renal failure (yes *versus* no)	<0.001	<0.001	-1.110	0.1114				
Hypertension (yes *versus* no)	0.65	0.35	-1.22	0.1670				
Disease duration (years)	1.02	0.99	-1.05	0.1319	1.05	1.02	-1.09	0.0024
Current smoker (yes *versus* no)	1.89	1.06	-3.36	0.0328				
Swollen joints (/28)	1.06	1.02	-1.11	0.0082				
Painful joints (/28)	1.03	1.00	-1.05	0.0342				
Patient VAS [0–100]	0.99	0.97	-1.00	0.0130				
ESR, mm, mean (SD)	1.011	1.000	1.023	0.0482	1.01	1.000	1.028	0.0499
DAS28	1.34	1.12	-1.62	0.0015				
Nodules (yes *versus* no)	1.98	1.01	-3.87	0.0502				
At least one new erosion (yes *versus* no)	1.66	1.04	-2.64	0.0351				
Morning stiffness (min)	1.01	1.00	-1.01	<0.0001				
HAQ score [0–3]	1.69	1.24	-2.31	0.0009				
SF36 PCS [0–100]	0.95	0.92	-0.98	0.0005	0.94	0.91	-0.98	0.0009
SF36 MCS [0–100]	0.97	0.95	-0.99	0.0020	0.97	0.95	-0.99	0.0193
Glucocorticoids (yes *versus* no)	1.76	1.08	-2.85	0.0202	2.36	1.30	-4.127	0.0046

95%CI: 95% confidence interval; VAS: visual analogue scale; DAS28: disease activity score on 28 joints, for RA; HAQ: health assessment questionnaire; SF36: short-form 36-item quality-of-life questionnaire; PCS: physical component summary of the SF36; MCS: mental component summary of the SF36; bivariate analysis for "renal failure (yes *versus* no)" was done with Fisher's exact test and exact confidence interval according to Cornfield's method; *n=342.

Table III. Spondyloarthritis patients, odds ratio and 95% confidence interval for the risk of receiving biologics in RA patients, by bivariate analyse.

Spondyloarthritis patients	Univariate				Multivariate*			
	Odds ratio	95%CI lower*	upper*	*p*-value	Odds ratio	95%CI lower*	upper*	*p*-value
Age (years)	0.98	0.95	-1.00	0.0486	0.96	0.93	-0.99	0.0058
Disease duration (years)	1.00	0.97	-1.03	0.8084				
Patient VAS [0–100]	0.97	0.95	-0.99	<0.0001				
CRP (mg/L)	1.01	0.99	-1.03	0.1924				
BASDAI [0–100]	1.04	1.02	-1.05	<0.0001				
Radiological progression (yes *versus* no)	0.41	0.17	-1.00	0.0412				
Morning stiffness (min)	1.01	1.01	-1.02	<0.0001				
HAQ score [0–3]	3.06	1.80	-5.22	<0.0001	2.92	1.45	-5.86	0.0026
SF36 PCS [0–100]	0.92	0.88	-0.96	<0.0001				
SF36 MCS [0–100]	0.96	0.93	-0.98	0.0011				
Glucocorticoids (yes *versus* no)	1.44	0.66	-3.15	0.3575				

95%CI: 95% confidence interval; VAS: visual analogue scale; CRP: C-reactive protein; BASDAI: Bath ankylosing spondylitis disease activity index, for SA; HAQ: health assessment questionnaire; SF36: short-form 36-item quality-of-life questionnaire; PCS: physical component summary of the SF36; MCS: mental component summary of the SF36.
*n=140.

nist therapy were younger age, longer disease duration, glucocorticoid use, and poorer quality of life.

In SA patients, the univariate analyses showed that factors associated with TNF-α antagonist therapy were younger age, higher disease activity (according to patient VAS, morning stiffness, BASDAI), previous radiographic progression, worse disability (HAQ), and poorer quality of life (SF36). In multivariate analysis, once worse disability (HAQ) and younger age were taken into account, no other factors appeared associated with TNF alpha antagonist therapy.

TNF-α antagonist therapy was used routinely in the JIA patients inadequately responsive to methotrexate, except those with contraindications (7%).

Physician-reported reasons for not initiating TNF-α antagonist therapy

The physicians reported that the main reason for not initiating TNF-α antagonist therapy in patients with RA or SA was low or stable disease activity,

Table IV. Reasons for not prescribing biologics in patients with rheumatoid arthritis or spondyloarthritis.

	RA	n=272	SA	n=90
Available data	221	82%	87	97%
Non rheumatologic contraindication	13	6%	6	7%
Refusal by the patient	21	10%	8	10%
Not indicated according to the physician, despite disease activity	18	8%	9	11%
Disease controlled according to physician	156	72%	56	67%
DAS28 (min - median - max)	2 - 4.8 - 9		-	-
BASDAI (min - median - max)	-	-	3 - 47.2 - 91	

RA: rheumatoid arthritis; SA: spondyloarthritis; DAS28: disease activity score on 28 joints; BASDAI: Bath ankylosing spondylitis index.

despite the DAS28 and BASDAI values indicating high disease activity. In only 10% of cases was the absence of TNF-α antagonist therapy initiation related to patient refusal. Non-rheumatological contraindications were present in 7% and 6% of RA and SA patients not given TNF-α antagonist therapy, respectively.

Discussion

This study shows that in France, where TNF-α antagonists are fully reimbursed by the national healthcare system, these drugs were prescribed routinely to JIA patients unresponsive to methotrexate, to about half of SA patients with BASDAIs ≥4 despite NSAID therapy, and to only a third of RA patients with DAS28>3.2 despite methotrexate therapy. Absence of TNF-α antagonist therapy was due to patient refusal in only 10% of cases and to contraindications in 6–7% of cases.

This study was limited to patients with active disease and naïve to biologics. We showed previously (12) that, among RA patients, 0.9% met British Society for Rheumatology (BSR) criteria and 7.0% SFR criteria for TNF-α antagonist therapy, whereas 10% were deemed eligible for TNF-α antagonists by their rheumatologist based on high disease activity (DAS28>5.1), ongoing structural progression, and elevated daily corticosteroid intake, all of which are among SFR criteria. In a Belgian study, 27.4% of methotrexate-experienced patients were eligible for biologics according to their rheumatologist (25). A study done in the UK found that 11% of RA patients had failed synthetic DMARD therapy and had no contraindications to TNF-α antagonists, suggesting eligibility for these last agents (26). However, only 5.6% of patients met BSR criteria for TNF-α antagonist therapy (which include DAS28>5.1) (26). These data suggest that criteria for using biologics may vary across countries. Nevertheless, in our patients who were started on TNF-α antagonists, disease activity was within the ranges reported in other countries (DAS28, 5.4±1.3 [min 3; max 9] in RA and BASDAI 60.5±20.5 [min 9; max 93] in SA). In previous cohorts of RA patients, DAS28 values ranged from 3.5 to 6.6 (27-31); and in SA patients, BASDAI values ranged from 61 to 76 (32-33).

Many factors may explain the low rate of biologic therapy, including co-morbidities, concern about risks and cost (34-38), and patient unwillingness to change their medications. However, the main reason for not using biologics in eligible patients in our study was low disease activity and/or severity as perceived by the physicians and/or patients. Data from the patient questionnaire indicated that most patients perceived their current physical state as acceptable, despite major physical limitations in performing everyday activities. In addition, although the DAS28 and BASDAI have been proven valid for guiding patient management, they may be viewed by physicians as having limited relevance. Both indices may be affected not only by damage due to long-standing disease, but also by other factors such as intraarticular injections or oral glucocorticoid therapy. Thus, a substantial proportion of patients treated for RA or SA still have active disease despite the availability of additional treatment options. The low percentage of patients treated by anti TNF was not explained by a spontaneous improvement after inclusion, but by physicians or patient's perception of the disease despite indices suggesting a high activity.

Another interesting finding is the low rate of nonrheumatological contraindications to TNF-α antagonists. These contraindications may have been under-recognised, as they may have been sought aggressively only in those patients deemed by the physicians to be potentially eligible for TNF-α antagonist therapy. Furthermore, contraindications may be less actively sought when reimbursement of TNF-α antagonists is unrestricted, as is the case in France. A retrospective analysis of semi-annual patient-reported data in a large observational cohort in the US (Arthritis, Rheumatism and Aging Medical Information System, ARAMIS) showed results similar to those from our study (29).

The first strength of this study is the nationwide, multispecialist, longitudinal, prospective design. However, although we obtained a sample of physicians from all French regions and various types of practices, we do not know whether these physicians were fully representative of all physicians caring for patients with RA, SA, and JIA in France. The second strength is that we included patients based on disease activity and not on prescription criteria. This point allowed us to assess the rates and reasons of not prescribing TNF-α antagonist therapy. Another strength of this study is that all questionnaires were fulfilled during a medical visit, and this methodology explain that all questionnaires were fully completed.

The main limitation of the study is that it was confined to a 3-year period (2007–2009). Prescription patterns change over time. For instance, the use of TNF-α antagonists to treat RA in France increased from 8% in 2003 to 16% in 2005 and 19% in 2007 (12). We cannot exclude a bias in the selection of patients depending on the physician's

acceptance to participate in the study but the available data about the type of centre, practice, and region of inclusion suggest a good representativity. We did not specified in the protocol that the signs of activity have to be documented on at least two occasions and this point may explain that physicians did not start anti TNF in some case. Another limit of the study is that we did not separate patients considered as having or not psoriatic arthritis among those suffering from spondyloarthritis. Nevertheless, in spondyloarthritis, the distinction between ankylosing associated to psoriasis to psoriatic arthritis with axial involvement remains unclear (39).

Conclusion

To conclude, in France where TNF-α antagonists are reimbursed without restrictions by the National Health insurance system, these drugs were prescribed routinely to patients with JIA unresponsive to methotrexate and were used in about half of SA patients with BASDAI≥4 and about a third of RA patients with DAS28>3.2 despite methotrexate therapy. In RA, younger age and poorer quality of life were strong determinants of TNF-α antagonist initiation than was higher disease activity.

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References

1. ROUX CH, SARAUX A, LE BIHAN E *et al*.: Rheumatoid arthritis and spondyloarthropathies: geographical variations in prevalence in France. *J Rheumatol* 2007; 34: 117-22.
2. SARAUX A, GUILLEMIN F, GUGGENBUHL P *et al*.: Prevalence of spondyloarthropathies in France: 2001. *Ann Rheum Dis* 2005; 64: 1431-5.
3. GUILLEMIN F, SARAUX A, GUGGENBUHL P *et al*.: Prevalence of rheumatoid arthritis in France: 2001. *Ann Rheum Dis* 2005; 64: 1427-30.
4. SOLAU-GERVAIS E, ROBIN C, GAMBERT C *et al*.: Prevalence and distribution of juvenile idiopathic arthritis in a region of Western France. *Joint Bone Spine* 2010; 77: 47-9.
5. VAN DEN BERG R, STANISLAWSKA-BIERNAT E, VAN DER HEIJDE DM: Comparison of recommendations for the use of anti-tumour necrosis factor therapy in ankylosing spondylitis in 23 countries worldwide. *Rheumatology* (Oxford) 2011; 50: 2270-7.
6. ZOCHLING J, VAN DER HEIJDE D, BURGOS-VARGAS R *et al*.; 'ASSESSMENT IN AS' INTERNATIONAL WORKING GROUP; EUROPEAN LEAGUE AGAINST RHEUMATISM: ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2006; 65: 442-52.
7. SAAG KG, TENG GG, PATKAR NM *et al*.: American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum* 2008; 59: 762-84.
8. SINGH JA, FURST DE, BHARAT A *et al*.: 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res* (Hoboken) 2012; 64: 625-39.
9. CURTIS JR, JAIN A, ASKLING J *et al*.: A comparison of patient characteristics and outcomes in selected European and U.S. rheumatoid arthritis registries. *Semin Arthritis Rheum* 2010; 40: 2-14.
10. CAPORALI R, SARZI-PUTTINI P, ATZENI F *et al*.: Switching TNF-alpha antagonists in rheumatoid arthritis: the experience of the LORHEN registry. *Autoimmun Rev* 2010; 9: 465-9.
11. PEASE C, POPE JE, THORNE C *et al*.: Canadian variation by province in rheumatoid arthritis initiating anti-tumor necrosis factor therapy: results from the optimization of adalimumab trial. *J Rheumatol* 2010; 37: 2469-74.
12. FAUTREL B, FLIPO RM, SARAUX A: Eligibility of rheumatoid arthritis patients for anti-TNF-alpha therapy according to the 2005 recommendations of the French and British Societies for Rheumatology. *Rheumatology* (Oxford) 2008; 47: 1698-703.
13. SARAUX A, DEVAUCHELLE-PENSEC V, ENGERRAN L, FLIPO RM: Most rheumatologists are conservative in active rheumatoid arthritis despite methotrexate therapy: results of the PRISME survey. *J Rheumatol* 2006; 33: 1258-65.
14. PHAM T, FAUTREL B, DERNIS E *et al*.: Recommendations of the French Society for Rheumatology regarding TNF-alpha antagonist therapy in patients with ankylosing spondylitis or psoriatic arthritis: 2007 update. *Joint Bone Spine* 2007; 74: 638-46.
15. FAUTREL B, PHAM T, MOUTERDE G *et al*.: Recommendations of the French Society for Rheumatology regarding TNF alpha antagonist therapy in patients with rheumatoid arthritis. *Joint Bone Spine* 2007; 74: 627-37.
16. VAN GESTEL AM, HAAGSMA CJ, VAN RIEL PLCM: Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis Rheum* 1998; 41: 1845-50.
17. GARRETT S, JENKINSON T, KENNEDY LG, WHITELOCK H, GAISFORD P, CALIN A: A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994; 21: 2286-91.
18. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
19. DOUGADOS M, VAN DER LINDEN S, JUHLIN R *et al*.: The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991; 34: 1218-27.
20. PETTY RE, SOUTHWOOD TR, BAUM J *et al*.: Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. *J Rheumatol* 1998; 25: 1991-4.
21. GUILLEMIN F, BRAINÇON S, POUREL J: Measurement of the functional capacity in rheumatoid polyarthritis: a French adaptation of the Health Assessment Questionnaire (HAQ)]. *Rev Rhum Mal Osteoartic* 1991; 58: 459-65.
22. POUCHOT J, RUPERTO N, LEMELLE I *et al*.: Paediatric Rheumatology International Trials Organisation. French Study Group for Quality of Life in Rheumatology. The French version of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ). *Clin Exp Rheumatol* 2001; 19 (Suppl. 23): S60-5.
23. PERNEGER TV, LEPLEGE A, ETTER JF, ROUGEMONT A: Validation of a French-language version of the MOS 36-Item Short Form Health Survey (SF-36) in young healthy adults. *J Clin Epidemiol* 1995; 48: 1051-60.
24. LEPLEGE A, ECOSSE E, VERDIER A, PERNEGER TV: The French SF-36 Health Survey: translation, cultural adaptation and preliminary psychometric evaluation. *J Clin Epidemiol* 1998; 51: 1013-23.
25. GEENS E, GEUSENS P, VANHOOF J *et al*.: Belgian rheumatologists' perception on eligibility of RA patients for anti-TNF treatment matches more closely Dutch rather than Belgian reimbursement criteria. *Rheumatology* (Oxford) 2009; 48: 546-50.
26. YEE CS, FILER A, PACE A, DOUGLAS K, SITUNAYAKE D, ROWE IF; WEST MIDLANDS RHEUMATOLOGY SERVICES AND TRAINING COMMITTEE: The prevalence of patients with rheumatoid arthritis in the West Midlands fulfilling the BSR criteria for anti-tumour necrosis factor therapy: an out-patient study. *Rheumatology* (Oxford) 2003; 42: 856-9.
27. HYRICH KL, LUNT M, WATSON KD, SYMMONS DP, SILMAN AJ; BRITISH SOCIETY FOR RHEUMATOLOGY BIOLOGICS REGISTER: Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. *Arthritis Rheum* 2007; 56: 13-20.
28. YAZICI Y, SHI N, JOHN A: Utilization of biologic agents in rheumatoid arthritis in the United States: analysis of prescribing patterns in 16,752 newly diagnosed patients and patients new to biologic therapy. *Bull NYU Hosp Jt Dis* 2008; 66: 77-85.
29. DEWITT EM, LIN L, GLICK HA, ANSTROM KJ, SCHULMAN KA, REED SD: Pattern and predictors of the initiation of biologic agents for the treatment of rheumatoid arthritis in the United States: an analysis using a large observational data bank. *Clin Ther* 2009; 31: 1871-80; discussion 1858.
30. HETLAND ML, CHRISTENSEN IJ, TARP U *et al*.; ALL DEPARTMENTS OF RHEUMATOLOGY IN

DENMARK: Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis Rheum* 2010; 62: 22-32.

31. KIEVIT W, FRANSEN J, ADANG EM *et al*.: Long-term effectiveness and safety of TNF-blocking agents in daily clinical practice: results from the Dutch Rheumatoid Arthritis Monitoring register. *Rheumatology* (Oxford) 2011; 50: 196-203.
32. ARENDS S, BROUWER E, VAN DER VEER E *et al*.: Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. *Arthritis Res Ther* 2011; 13: R94.
33. LORD PA, FARRAGHER TM, LUNT M, WATSON KD, SYMMONS DP, HYRICH KL; BSR BIOLOGICS REGISTER: Predictors of response to anti-TNF therapy in ankylosing spondylitis: results from the British Society for Rheumatology Biologics Register. *Rheumatology* (Oxford) 2010; 49: 563-70.
34. BRAUN J, SIEPER J: Remission and possible discontinuation of biological therapy in axial spondyloarthritis. *Clin Exp Rheumatol* 2013; 31 (Suppl. 78): S33-6
35. SONG IH, HAIBEL H, PODDUBNYY D, BRAUN J, SIEPER J: Withdrawal of biologic therapy in axial spondyloarthritis: the experience in early disease. *Clin Exp Rheumatol* 2013; 31 (Suppl. 78): S37-42.
36. RAMÍREZ-HERRÁIZ E, ESCUDERO-VILAPLANA V, ALAÑÓN-PLAZA E *et al*.: Efficiency of adalimumab, etanercept and infliximab in rheumatoid arthritis patients: dosing patterns and effectiveness in daily clinical practice. *Clin Exp Rheumatol* 2013; 31: 559-65.
37. BERESNIAK A, BAERWALD C, ZEIDLER H *et al*.: Cost-effectiveness simulation model of biologic strategies for treating to target rheumatoid arthritis in Germany. *Clin Exp Rheumatol* 2013; 31: 400-8.
38. CECCARELLI F, PERRICONE C, TROTTA F *et al*.: Remission in early, aggressive rheumatoid arthritis: a multicentre prospective observational Italian study ARPA (Artrite Reumatoide Precoce Aggressiva). *Clin Exp Rheumatol* 2013; 31: 341-9.
39. RICHETTE P, TUBACH F, BREBAN M *et al*.: Psoriasis and phenotype of patients with early inflammatory back pain. *Ann Rheum Dis* 2013; 72: 566-71.