Application of Recommendations Regarding the Use of Subcutaneous Tumor Necrosis Factor Inhibitors in Spondyloarthritis by Rheumatologists in Daily Practice

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ABSTRACT. ***Objective.*** To assess the implementation of European recommendations for use of TNF inhibitors for spondyloarthritis (SpA), rheumatologists' level of knowledge of and adherence to the recommendations, and potential barriers to the application of recommendations.

Methods. We conducted a retrospective study among 42 rheumatologists who initiated a first subcutaneous TNF inhibitor for SpA in 2013 or 2014. Thirty items from national and international recommendations were separated into 3 domains: indication, pretherapeutic monitoring, and management under TNF inhibitors. A standardized data collection procedure was used to gather data from medical files to assess the application of each recommendation. Questionnaires assessing the knowledge, level of adherence to each recommendation, and potential barriers to their implementation were sent to rheumatologists.

Results. Rheumatologists applied a mean of 60% of items from domains A and B, but less than 50% from domain C items. Recommendations regarding the search for previous infection and the prevention of future infections were the ones most often applied. However, < 60% of rheumatologists assessed cancer and other diseases before TNF inhibitor initiation. More than 95% of rheumatologists knew of the recommendations and had a high level of adherence. Lack of time, difficulties accessing specialized consultations, and lack of flexibility in the recommendations explained rheumatologists' difficulties in applying the recommendations.

Conclusion. Despite high levels of knowledge of, and adherence to, recommendations for using TNF inhibitors for SpA, rheumatologists' application was limited because of a lack of human and material resources. (J Rheumatol First Release February 1 2018; doi:10.3899/jrheum.170587)

Key Indexing Terms:
TUMOR NECROSIS FACTOR INHIBITORS
SPONDYLOARTHRITIS
RECOMMENDATIONS
RHEUMATOLOGISTS' PRACTICES

Clinical recommendations help practitioners change their practices, and improve health outcomes and cost-effectiveness. The implementation of recommendations is the process by which clinicians integrate recommendations into their practice[1]. Despite their wide distribution, promotion, and clinicians' good adherence, recommendations are often not extensively used, and barriers to their implementation have been reported[2].

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Tumor necrosis factor (TNF) inhibitors have demonstrated efficacy for spondyloarthritis (SpA), but they are expensive and could be responsible for severe side effects. To help practitioners care for patients with SpA, national and international recommendations have been established by the French Society of Rheumatology (SFR), the Club Rhumatisme et Inflammation (CRI), the French National Authority for Health (HAS), and the ASessment of Ankylosing Spondylitis (ASAS)/EUropean League Against Rheumatism (EULAR)[3,4,5,6,7].

These recommendations were disseminated through publications in national and international reviews, annual meetings, and the CRI Website. The CRI Website, well known by French rheumatologists, provides checklists on the use of biotherapies, based on published recommendations. However, we lack data on the implementation of these recommendations.

Our objectives were to assess the following: (1) rheumatologists' implementation of the updated recommendations for using TNF inhibitors for SpA; (2) their knowledge of, and adherence to, these recommendations; and (3) potential barriers to the implementation of the recommendations.

MATERIALS AND METHODS

We conducted a multicenter study among academic and private-practice rheumatologists who collaborated with 3 public hospitals (Orleans, Tours, and Blois) in the Centre-Val de Loire region, France. Forty-five rheumatologists were solicited who had prescribed a TNF inhibitor and/or followed patients receiving a TNF inhibitor. In January 2015, we mailed each rheumatologist a letter informing them about the study and asking them to participate.

Consenting rheumatologists provided us with the following: (1) the names of their SpA patients > 18 years old who had received their first TNF inhibitor in subcutaneous form between January 1, 2013, and December 31, 2014; and (2) patients' medical files, including imaging, biological results, and medical observation. To obtain the most exhaustive list of patients, we also included patients who were seen by an educational nurse before initiation of the first TNF inhibitor in Orleans and Tours hospitals. We included patients exclusively taking subcutaneous TNF inhibitors to avoid selection bias between private and academic practices. Each patient received a mailed information letter, with the possibility of refusing participation in the study. We excluded patients who participated in another clinical study.

Our study included 2 assessments to achieve our objectives: (1) rheumatologists' implementation of recommendations determined from patients' medical files; and (2) rheumatologists' knowledge and adherence to the recommendations and barriers to their implementation, measured using mailed questionnaires.

The protocol was approved by the ethics committee of Orleans Hospital in November 2014 (CE 2014-03).

Assessment of the implementation of recommendations and data collection. A set of 30 items was established by 2 rheumatologists (CS and CPG; Table 1). This set is based on published national and international recommendations from rheumatological societies such as ASAS/EULAR, SFR, and HAS[3,4,5,6,7].

The items corresponded to 3 domains: (A) indication for TNF inhibitors (items 1–4); (B) pretherapeutic monitoring (items 5–26); and (C) management under TNF inhibitors (items 27–30). Three independent rheumatologists (CP, MM, and CS) used a standardized form to collect anonymized data from patient files. Patients' characteristics and the application (yes/no) of the 30 domain items were collected. We considered every criterion that was not reported in the patient's file as "non-applied."

Assessment of knowledge of, and adherence to, the recommendations and barriers to their implementation in clinical practice. Between May 1 and June 30, 2015, 2 questionnaires were sent by mail to rheumatologists who agreed to participate. The first assessed rheumatologists' knowledge of the 30 domain items (yes/no) and their level of adherence to them (scale 0–10). It also collected demographic and practice characteristics of rheumatologists. The second questionnaire assessed the potential barriers to the implementation of the recommendations in clinical practice. Rheumatologists were asked to answer yes or no to a list of potential barriers that were based on literature data and our own experience[8,9].

Statistical analysis. Descriptive analyses were used to describe patients and rheumatologists. The application and knowledge of and level of agreement with the recommendations were analyzed by percentages for qualitative variables (with 95% CI) and means (with SD and range of minimal and maximal values) for continuous variables.

RESULTS

Response rate and samples. Among the 45 solicited rheumatologists, 42 (93.3%) agreed to participate and provided the names of their patients with SpA (Figure 1). In total, 211 patients were identified, and they received an information letter by mail. No patient refused to participate. All were adults (age > 18 yrs) with a diagnosis of SpA and had received their first TNF inhibitor in 2013 (n = 111) or 2014 (n = 100). Characteristics of the 211 patients are in Supplementary Table 1 (available from the authors upon request).

Each rheumatologist included a mean of 6.9 patients (SD = 1.1; range 1–25) in our study. Adalimumab was initiated in 40.8% of patients, etanercept in 36.5%, and golimumab in 22.7%; 78.2% of patients received a first prescription of a TNF inhibitor from a public-practice rheumatologist (after outpatient visits or hospitalizations; Supplementary Table 1, available from the authors upon request).

In total, 31/42 rheumatologists (73.8%) answered at least 1 mailed questionnaire. Their characteristics are in Table 2.

Domain A: TNF inhibitor indication. Overall, 30 of the 42 rheumatologists initiated a first TNF inhibitor (Table 3). The mean (SD) application of recommendations by rheumatologists was 59.6% (3.8) for the items in Domain A: diagnosis of SpA according to ASAS or New York classification criteria and high disease activity (according to Bath Ankylosing Spondylitis Disease Activity Index or Ankylosing Spondylitis Disease Activity Score index) despite optimal treatments [nonsteroidal antiinflammatory drugs (NSAID) or synthetic disease-modifying antirheumatic drugs]. The diagnosis was according to the rheumatologist's expertise for 40.4% of cases. High disease activity had been assessed twice in 2 months by the rheumatologist in less than one-third of cases.

Domain B: TNF inhibitor pretherapeutic monitoring. The application of the items in this domain was < 50% for the assessment of ongoing infection, clinical adenopathy, cancer symptoms, search for autoimmune disease and demyelinating disease, and lung disease (Table 3). Items related to tuberculosis screening, viral serology, updated vaccinations, the search for previous or ongoing malignancy, and pregnancy were well applied (rate > 60%).

Domain C: Management under TNF inhibitors. Almost 50% of patients were cared for by a hospital practitioner, 15.6% by a private-practice rheumatologist, and 34.6% by rheumatologists with both practices. The recommended first followup time (12–16 wks) was completed by rheumatologists for < 50% of the cases (Table 3). Nevertheless, the mean (SD) time between initiation of the TNF inhibitor and the first followup visit was 14 weeks [0.4; median 12.9 weeks (range 3–43.4)]. The tolerance of TNF inhibitors was well assessed (80% of cases), but disease activity (NSAID intake and Bath Ankylosing Spondylitis Disease Activity Index) was monitored in < 50% of cases. We found no significant difference between 2013 and 2014 results (Supplementary Table 2, available from the authors upon request).

Rheumatologist's knowledge of and adherence to the recommendations. Between 93 and 100% of the 31 rheumatologists who answered the questionnaire stated that they knew recommendations (Table 4). Their mean agreement with the recommendations was high, from 9.1 to 10, out of 10.

Table 1. Thirty items selected from the national and international recommendations for TNF inhibitors for SpA[3,4,5,6,7].

Domain A: Indications for TNF inhibitors		
Indications	1	SpA diagnosis according to ASAS or New York modified criteria
	2	Active disease for ≥ 4 wks, expressed by BASDAI ≥ 4 or ASDAS ≥ 2.1 for axSpA; or ≥ 3 swollen and tender joints or coxitis, destructive or persistent arthritis for articular SpA; or a score of ≥ 5/10 on VAS for pain for enthesitic SpA
	3	Active disease ≥ 4 wks
	4	Failure of prior treatment with ≥ 2 NSAID for ≥ 4 wks for axial disease and ≥ 1 DMARD or local injection for peripheral disease
Domain B: Pretherapeutic monitoring		
Infections	5	Detection of TB infection by tuberculin skin test or QFT
	6	Prescription of a chest radiograph for the pretherapeutic monitoring
	7	Research of active infection clinical signs (medical history and physical examination)
	8	Prescription of HIV serology for pretherapeutic monitoring
	9	Prescription of hepatitis B and C serology for pretherapeutic monitoring
	10	Checking for updated antitetanus vaccination
	11	Suggestion for antipneumococcal vaccination, every 3–5 yrs
	12	Suggestion for seasonal antiinfluenza vaccination
	13	Clinical evaluation of the dental status ± dentist consultation for dental care before starting TNF inhibitors
Neoplasia	14	Research of personal medical history of cancer
	15	Checking for cancer screening (gynecologist, prostate, colon, etc.)
	16	Research of adenopathy and malignant blood disease sign (medical history and physical examination)
	17	Research of solid cancer sign (medical history and physical examination)
	18	Prescription of a blood count for the pretherapeutic monitoring
	19	Prescription of serum protein electrophoresis test for the pretherapeutic monitoring
Multiple sclerosis	20	Research of multiple sclerosis, optic neuritis, or demyelinating disease (personal or family history)
	21	Research of demyelinating disease sign (physical examination)
Autoimmune diseases	22	Research of medical history of autoimmune disease (lupus, hepatitis, vasculitis)
	23	Research of antinuclear antibodies in blood for the pretherapeutic monitoring
Cardiopulmonary	24	Research of clinical sign or personal history of chronic lung disease
	25	Research of clinical signs or personal history of chronic heart disease
Pregnancy	26	Research of desire for pregnancy, ongoing pregnancy, or contraception treatment
Domain C: Monitoring under TNF inhibitors		
	27	First followup after initiation of TNF inhibitors between 12 and 16 wks
	28	Use of an activity score (BASDAI, ASDAS, BASFI, DAS) to monitor the SpA activity
	29	Monitoring of NSAID use
	30	Monitoring of tolerance of the TNF inhibitors

TNF: tumor necrosis factor; SpA: spondyloarthritis; ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial SpA; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; VAS: visual analog score; NSAID: nonsteroidal antiinflammatory drug; DMARD: disease-modifying antirheumatic drug; TB: tuberculosis; QFT: quantiFERON-TB test; HIV: human immunodeficiency virus; BASFI: Bath Ankylosing Spondylitis Functional Index; DAS: Disease Activity Score; ASAS: Assessment of Spondyloarthritis international Society.

Main barriers to the application of recommendations. For domain A (indication for TNF inhibitors), the main reported barriers to implementation were lack of flexibility regarding patient specificities for 31% of participants (e.g., character-

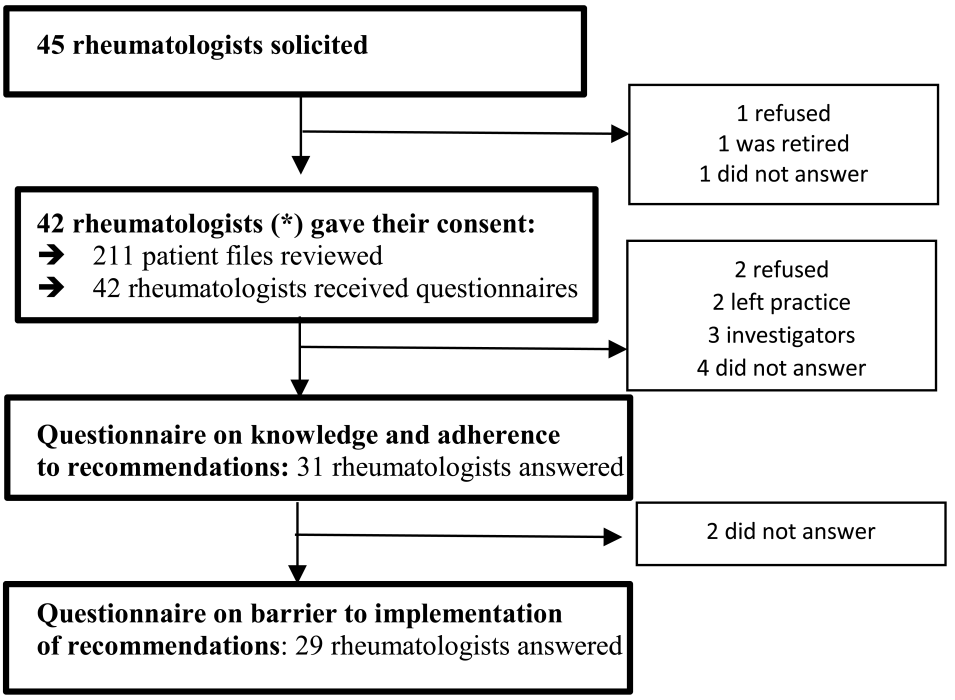

Figure 1. Flow chart of rheumatologists in the study. * 15 rheumatologists were in Loiret (58 patients), 20 in Indre-et-Loire (124 patients), 4 in Loir-et-Cher (24 patients), 2 in Indre (4 patients), and 1 in Cher (1 patient). Fifteen worked with Orleans hospital, 23 with Tours hospital, and 4 with Blois hospital. Rheumatologists from Indre and Cher worked with Tours hospital.

istics, comorbidities) and lack of time during the visit for 25%. For domain B (pretherapeutic monitoring), 41.4% of rheumatologists reported a lack of access to specialists before treatment, and 27.6% pointed to patients' lack of knowledge of their medical history as barriers to application. For domain C (management under TNF inhibitors), 41.4% and 31% of rheumatologists reported the delay between 2 rheumatologic visits and lack of flexibility in recommendations regarding patients' specificities as barriers, respectively. They also reported difficulties in patient education (31%; data not shown).

DISCUSSION

We found that rheumatologists did not extensively apply recommendations for the use of TNF inhibitors for SpA, despite their self-reported good knowledge of them and agreement with them. Some barriers reported by the practitioners included lack of access to specialized physicians before the initiation of therapy, lack of time during the visit, the delay between 2 visits, and lack of adaptability of the recommendations to clinical practice.

We observed good application of the recommendations regarding the biological and imaging pretherapeutic examination, which took less consulting time than items requesting clinical examination. It follows from this that the lack of time during the visit is a major impediment to good practices. The application of recommendations was also satisfactory but lower for the disease-monitoring items, and the self-declared application of recommendations was higher than ours in the Gossec, *et al* study of the 2006 ASAS/EULAR recommendations[8]. However, the application of a recommendation regarding the assessment of comorbidities in patients with SpA was < 51% in the Moltó, *et al* international study (data collected from medical records and during patient interviews), except for hepatitis B and C virus serology, and dental evaluation[10].

The results regarding the knowledge of and agreement with recommendations are close to those previously published for the 2006 and 2010 ASAS/EULAR recommendations on the indication for TNF inhibitors in SpA[8,11,12].

We also found a gap between the agreement of rheumatologists with the recommendations and their real-life implementation. The 2008 international study by Gossec, *et al*[8] had the same findings. External factors may influence rheumatologists' practices and their adherence to recommendations, as suggested by Spadaro, *et al*[13].

Factors such as the lack of human or material resources, lack of time during the medical visit, or lack of flexibility of the recommendations were already highlighted in 2 previous international studies[8,9]. In our study, the interviewed rheumatologists reported the same factors with similar rates. Thus, despite many proposals to improve the implementation of the

Table 2. Rheumatologists' characteristics. Values are n (%), (95% CI) unless otherwise specified.

Characteristics	Values
Rheumatologist participation, n (%)*	31/45 (73.8)
Age, yrs, mean ± SD°	48.8 (2.1)
Duration of medical practice, yrs, mean ± SD°	17.7 (2.1)
Sex*	
Men	17 (40.5), (25.6–55.3)
Women	25 (59.5), (44.7–74.4)
Practice*	
Hospital	20 (47.6), (32.5–62.7)
Hospital + private	9 (21.4), (9.0–33.8)
Private	13 (31.0), (17.0–44.9)
City of practice*	
Orléans	15 (35.7), (21.2–50.2)
Tours	20 (47.6), (32.5–62.7)
Blois	4 (9.5), (0.6–18.4)
Châteauroux	2 (4.8), (0.0–11.2)
Bourges	1 (2.4), (0.0–7.0)
Medical training°	
Meetings	
SFR	28 (93.3), (84.4–100.0)
EULAR	17 (56.7), (38.9–74.4)
ACR	9 (30.0), (13.6–46.4)
None	1 (3.3), (0.0–9.8)
Rheumatological literature	
French	28 (90.3), (79.9–100.0)
English	16 (51.6), (34–69.2)
None	1 (3.2), (0–9.5)
Workshops	29 (96.7), (90.2–100.0)
E-learning	21 (72.4), (56.1–88.7)

*Calculated for the 42 included rheumatologists. °Calculated for the 31 rheumatologists who answered the questionnaire. ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; SFR: French Society of Rheumatology.

Table 3. Rheumatologists' application of recommendations regarding indications for TNF inhibitors for SpA, pretherapeutic monitoring, and management under TNF inhibitors (assessment of 211 patient files).

Variables	Mean % ± SD
Domain A: Indications for TNF inhibitors	
Diagnosis of SpA according to classification criteria*	59.6 ± 3.8
Active disease	77.6 ± 5.7
Active disease ≥ 4 wks	31.7 ± 5.5
Despite optimal treatment	78.7 ± 3.9
Domain B: Pretherapeutic monitoring	
Infection	
TB detection	99.9 ± 0.1
Chest radiograph	93.3 ± 2.7
Ongoing infection	46.2 ± 6.5
Blood count	95.5 ± 2.1
HIV serology	79.8 ± 5.6
Hepatitis B and C serologies	93.1 ± 2.3
Tetanus vaccine	87.8 ± 4.3
Pneumococcal vaccine	83.8 ± 4.3
Influenza vaccine	60.8 ± 6.1
Dental status	61.4 ± 6.7
Neoplasia	
Cancer history	62.8 ± 6.5
Cancer screening	52.9 ± 6.6
Adenopathy	23.9 ± 5.6
Cancer symptoms	33.7 ± 6.0
SPEP test	74.7 ± 5.4
MS	
MS history	49.1 ± 7.0
Search for demyelinating disease	28.5 ± 6.2
Autoimmune diseases	
Search for autoimmune disease	39.2 ± 5.6
ANA	69.9 ± 4.9
Heart/lung diseases	
Pulmonary disease	48.4 ± 7.0
Heart disease	53.6 ± 6.9
Pregnancy	64.2 ± 7.2
Domain C: Management under TNF inhibitors	
First visit 12 to 16 weeks after TNF-inhibitor initiation ± 1 wk	48.7 ± 5.6
BASDAI assessment	33.3 ± 5.3
NSAID intake	49.1 ± 5.3
Safety assessment	80.0 ± 5.3

*ASAS or modified New York classification criteria. TNF: tumor necrosis factor; SpA: spondyloarthritis; ASAS: Assessment of Spondyloarthritis international Society; TB: tuberculosis; HIV: human immunodeficiency virus; SPEP: serum protein electrophoresis; MS: multiple sclerosis; ANA: antinuclear antibodies; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; NSAID: nonsteroidal antiinflammatory drug.

recommendations, there is still no satisfactory approach to counter these barriers to good practices.

Our study has several strengths. The participation rates of rheumatologists and patients were very good. No patient refused to participate in our study. Our rheumatologist sample is representative of the rheumatologist practice (in demographics and practice type) in the Centre-Val de Loire region, France[14,15]. The use of a patient education register allowed us to obtain a more exhaustive list of patients who received TNF inhibitors around the 2 hospital centers of Orleans and Tours.

To assess the application of recommendations by rheumatologists, the retrospective data collection avoided assessment bias. Indeed, the rheumatologists' practices were not affected, and the data collection was objective. This collection represents a strength as compared with other studies for which assessment of the implementation of recommendations was based on a self-declared questionnaire[8]. We also had few missing data: every rheumatologist gave us total access to the complete patient files, including imaging or biological tests, medical records, and observation. The number of patients that each rheumatologist had in our study varied greatly, from 1 to 25. To avoid bias related to a "rheumatologist effect" (i.e., rheumatologists who included the largest numbers of patients from their practice), we calculated the mean (SD) of patients per rheumatologist for whom each item has been completed.

Our study had some limitations. Retrospective data collection might have biased our results. We might have underestimated the rate of followed recommendations that required a clinical examination. Indeed, rheumatologists did not always report a physical examination in the patient file

Table 4. Rheumatologists' knowledge and adherence to recommendations (n= 31).

Recommendations	Knowledge			Adherence		
	n (m)	%	95% CI	m	Mean	SD
Domain A: Indications for TNF inhibitors						
Indications						
Modified New York/ASAS classification criteria	31	100	100.0–100.0		9.1	0.28
Active disease ≥ 4 wks	30	96.8	90.6–100.0		9.6	0.21
Domain B: Pretherapeutic monitoring						
Infection						
Ongoing infection	31	100	100.0–100.0	1	9.8	0.18
Assessment of high risk of infection	30	96.8	90.6–100.0	1	9.5	0.24
HIV serology	30	96.8	90.6–100.0		9.8	0.16
Hepatitis B serology	31	100	100.0–100.0		10.0	0.03
Hepatitis C serology	31	100	100.0–100.0		10.0	0.03
Pneumococcal vaccine	30	96.8	90.6–100.0		9.6	0.30
Tetanus vaccine	31	100	100.0–100.0		9.8	0.09
Influenza vaccine	30 (1)	100	100.0–100.0	2	9.7	0.19
Dental status	31	100	100.0–100.0		9.8	0.10
Cancer						
Cancer screening	29 (1)	96.7	90.2–100.0	1	9.5	0.23
Research of hemopathy/adenopathy	29 (1)	96.7	90.2–100.0	1	9.9	0.09
Research of cancer or precancer	30 (1)	100	100.0–100.0	3	9.6	0.23
Pregnancy	31	100	100.0–100.0		9.4	0.24
Other						
Autoimmune disease/MS	30	96.8	90.6–100.0	1	9.2	0.29
Domain C: Management under TNF inhibitors						
Management						
First visit after 12 to 16 wks of anti-TNF	29 (2)	100	100.0–100.0	2	9.9	0.08
Safety assessment	29 (1)	96.7	90.2–100.0	2	9.8	0.15
Disease activity assessment	28 (1)	93.3	84.4–100.0	2	9.0	0.30

m: missing data; ASAS: Assessment of Spondyloarthritis international Society; HIV: human immunodeficiency virus; MS: multiple sclerosis; TNF: tumor necrosis factor.

when there was no problem, and we considered the recommendation as not applied if the information was absent.

In France, and particularly in the Centre-Val de Loire region, the lack of time and delay between 2 medical visits might increase in the future owing to the retirement of numerous medical doctors (estimated –3.7% of rheumatologists between 2007 and 2016)[14,15,16]. The collaboration between rheumatologists and nurses with skill in rheumatology could be an answer to this issue. Nurses might be in charge of disease activity monitoring, prebiologic checklist, assessment of comorbidities, vaccine updating, and patient education. As recommended by EULAR, such specialized nurses already practice with success in the United States, Canada, and the Netherlands[17]. Previous studies demonstrated that trained nurses were as efficient as medical doctors in assessing clinical disease activity for chronic inflammatory rheumatism[18]. Moreover, nurse outpatient visits led to healthcare cost reduction and increased rheumatologist consulting time dedicated to patients with high disease activity[19,20,21].

We demonstrated that despite high levels of knowledge of and adherence to recommendations for using TNF inhibitors for SpA, their application by rheumatologists is still limited, mostly because of lack of human and material resources, especially for disease monitoring.

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