Management of Infusion Reactions to Infliximab in Patients with Rheumatoid Arthritis or Spondyloarthritis: Experience from an Immunotherapy Unit of Rheumatology

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ABSTRACT. ***Objective.*** To suggest recommendations for management of acute infusion reactions induced by infliximab in patients with rheumatoid arthritis (RA) and spondyloarthritis (SpA).

Methods. In total, 203 patients were treated with infliximab (120 ml/h). Prevalence of acute infusion reaction was evaluated. To manage these conditions, recommendations were devised according to the type and the severity of clinical manifestations, which were classified beforehand in 2 groups: A (hypertension, pruritus, sudden flush, vomiting, tachycardia or bradycardia, shivers, fever) and B (urticaria, tickling throat, Quincke's edema, dyspnea, and hypotension). Recommendations were based mainly on adjustment of the infusion rate.

Results. It was observed that 23/203 patients (11.3%) had acute infusion reactions. Among them and prior to our recommendations, infliximab was completely discontinued in 8/23 patients. After our recommendations were implemented, 15/23 patients presented an acute infusion reaction: 8 and 7 patients with symptoms of Group A and B, respectively. In Group A (8 patients), reducing the infusion rate to 60–80 ml/h led to disappearance of symptoms; the modified treatment was then maintained. In Group B (7 patients), the infusion was immediately stopped and appropriate drugs were administered. Once clinical manifestations were alleviated, the infusion was resumed (60 ml/h). Prior to subsequent infusions (60 ml/h), a premedication was administered.

Conclusion. Based on these recommendations, infliximab could be maintained with great efficacy on disease activity in every patient with an acute infusion reaction. Our recommendations permit sustained administration of infliximab and allow every patient to benefit from this therapy. (First Release June 1 2006; J Rheumatol 2006;33:1307–14)

Key Indexing Terms:
INFLIXIMAB INFUSION REACTIONS RHEUMATOID ARTHRITIS
SPONDYLOARTHRITIS INFUSION RATE

Infliximab (INF) is a very effective treatment in patients with rheumatoid arthritis (RA) or spondyloarthritis (SpA). However, in some cases, this treatment has to be discontinued due to infusion reactions. Affected patients present various conditions: (1) acute systemic reactions, i.e., pruritus, urticaria, Quincke's edema, hypotension, hypertension, bradycardia, tachycardia, anaphylactoid shock, and fever during the infusion or within the next 2 hours[1]; (2) delayed systemic reactions within days after INF infusion that include arthralgia and joint stiffness[1]. Acute hypersensitivity infusion reactions have been described in 19% of patients with RA treated with INF compared to patients given a placebo[2]. Wasserman *et al* reported 8.8% of acute infusion reactions[3]. Infusion reactions usually occur during the first set of infusions[4]. The risk of such a reaction has been reduced, since INF is associated with immunosuppressive drugs[4,5].

However, the physiopathology of these acute reactions remains unknown, and no recommendations are currently available for the management of infusion reactions to INF. Prior to this study, we stopped INF infusions whenever such symptoms occurred. For some time, INF was the single tumor necrosis factor-α (TNF-α)-blocking agent available in France, and hence therapeutic maintenance was one of the primary goals. When INF was discontinued in patients who developed hypersensitivity reactions despite its efficacy for symptoms, we were prompted to develop recommendations that would help maintain this therapy. To achieve this, we designed a prospective study: the first step was to inventory symptoms observed following the first infusion reactions. Then, in the absence of any pathogenic explanation for their occurrence, these symptoms were pragmatically classified into 2 groups,

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A or B, which allowed us to develop procedures to manage acute reactions in either group. Overall, the objective of this study was the implementation and evaluation of these recommendations, which are based on modulation of the infusion flow according to the type and the severity of symptoms, in patients with RA or SpA treated with INF.

MATERIALS AND METHODS

Protocol for management of infusion reactions. The inventory of symptoms and signs observed during the first infusion reactions was carried out in the Rheumatology Department of Rouen University Hospital. In the absence of pathogenic explanations for their occurrence, reactions were arbitrarily divided into groups A and B, according to type and severity. Group A included symptoms of hypertension, pruritus, erythema and/or sudden flush, nausea and/or vomiting, lumbar pain and/or myalgia, shivers and/or fever. Group B included state of shock, larynx irritation and/or labial edema, Quincke's edema, urticaria, dyspnea, hypotension, and distress. Patients could present with some symptoms of Group A and Group B.

We formulated precise recommendations for each well defined symptom that would be easy to use in routine practice by nurses involved in primary care, who are the first to be confronted with infusion reactions. For symptom management, we focused on the modulation of flow infusion with 2 possible situations: (1) reducing the infusion flow (down to 80 ml/h or 60 ml/h) if the patient had a sudden flush, fever, pruritus, nausea, or increased blood pressure; and (2) interrupting the infusion and establishing another venous access in cases of Quincke's edema, facial edema, urticaria, throat irritation or thoracic pain, dyspnea, state of shock, or hypotension (Figures 1 and 2). After these procedures were initiated by nursing staff, the physician was immediately called to carry out the following steps. If the patient (with Group A symptoms) had not improved following the flow reduction, symptomatic treatment (anti-H1 or acetaminophen or calcium inhibitor) was prescribed. For Group B symptoms (with the exception of Quincke's edema, hypotension, and shock), intravenous (IV) methylprednisolone (1 mg/kg) and/or dexchlorpheniramine were required, and a premedication with anti-H1 (cetirizine) was administered 2 days prior to and 3 days after INF infusion. Dexchlorpheniramine was used when patients first experienced urticaria. Steroids were administered either after the failure of dexchlorpheniramine or directly for Quincke's edema, anaphylactoid shock, hypotension, and wheezing. When a patient presented with Quincke's edema, the INF infusion was to be stopped immediately and treatment was to be prescribed by the physician (e.g., methylprednisolone, oxygen, cardiopulmonary resuscitation). When a patient presented with symptoms from both Group A and B, the procedure established for Group B symptoms was used (Table 1).

Patients. A total of 203 consecutive patients with RA or SpA treated with INF infusions in the immunotherapy unit of the Rheumatology Department between January 2000 and December 2003 were included in the study. These patients were followed until October 2005. The patients fulfilled the criteria of the American College of Rheumatology and the European Spondylarthropathy Study Group[6,7]. These patients were treated with INF when conventional disease modifying antirheumatic drugs including methotrexate and/or sulfasalazine failed to control disease. For RA patients, INF was associated with methotrexate or leflunomide according to the recommendations for INF therapy. For SpA patients, INF was administered alone according to the ASsessments in Ankylosing Spondylitis Working Group consensus statement[8]. For each patient data were collected according to the disease, demographics (sex, age), clinical findings [disease duration, morning stiffness, tender joint count, swollen joint count, patient's assessment of pain and disease

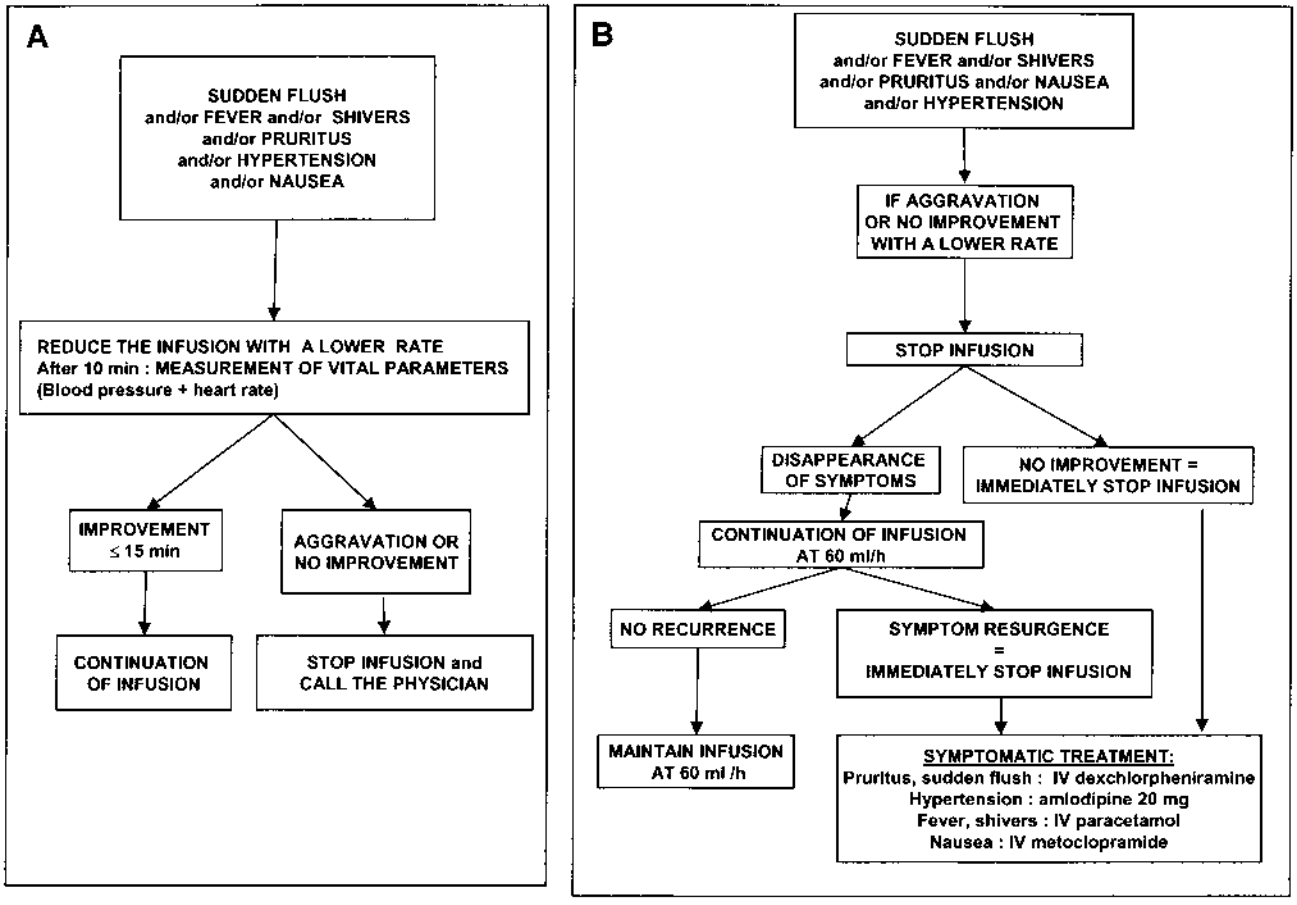

Figure 1. A. Options for nurses confronted with Group A symptoms. B. Options for physician confronted with Group A symptoms.

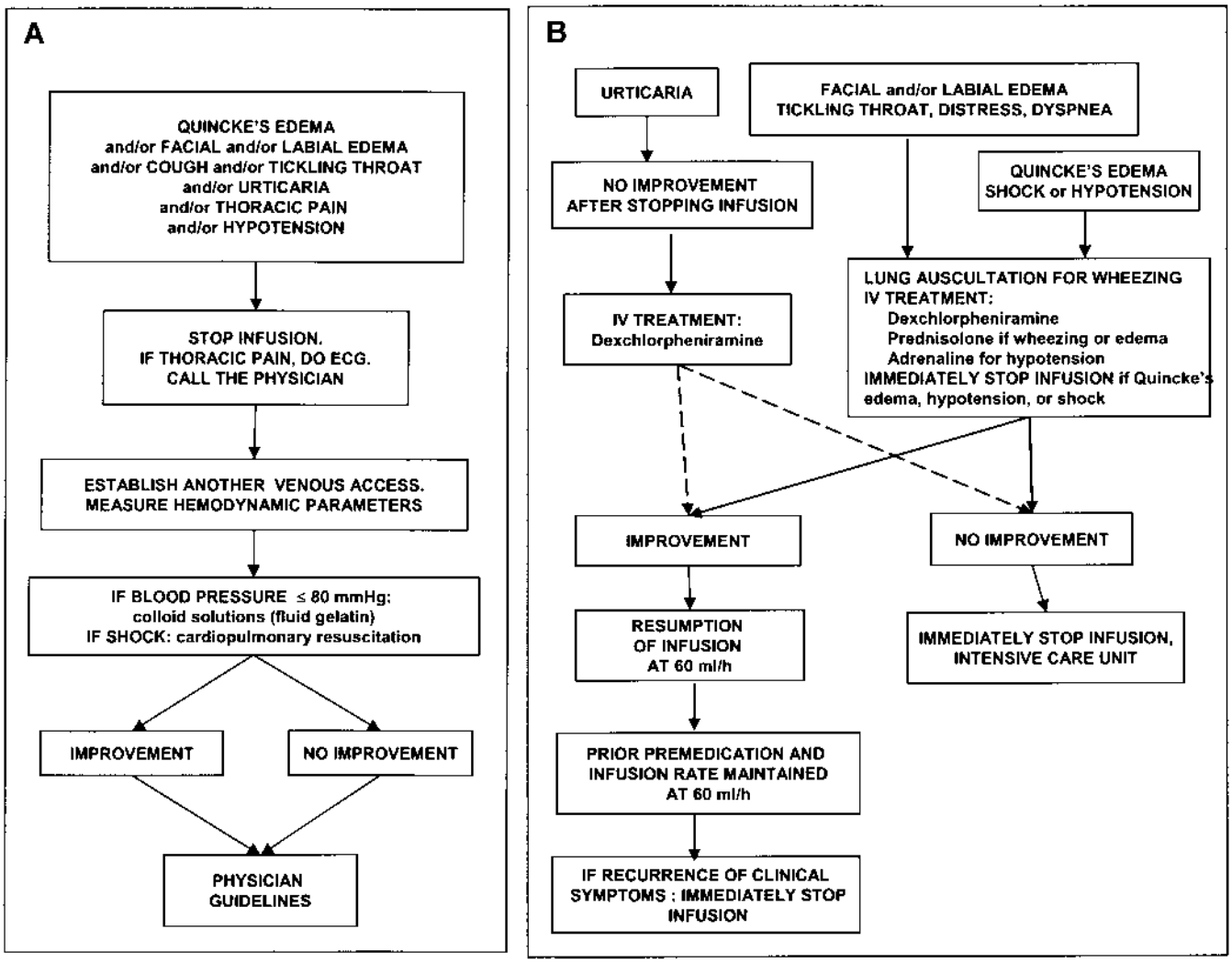

Figure 2. A. Options for nurses confronted with Group B symptoms. B. Options for physician confronted with Group B symptoms. ECG: electrocardiogram.

activity, Disease Activity Score-28 (DAS28), treatment], and laboratory results [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), latex and Waaler-Rose tests, antinuclear antibodies (ANA)].

INF infusions. For RA and SpA patients, the standard doses of INF were 3 mg/kg or 5 mg/kg, respectively, given IV over a 2-hour period at 0, 2, 6, and 14 weeks and every 2 months thereafter. INF infusions were delivered with a pump that allowed modulation of the infusion flow. For every patient, the initial flow was 120 ml/h and blood pressure and heart frequency were monitored. When confronted with an acute infusion reaction during the supervision, the nurse referred to recommendations (stopping infusion, measuring blood pressure and heart frequency) as a first step of the procedure and then immediately alerted the physician (Figures 1 and 2).

Statistical analysis. Comparisons of demographic, clinical, and biological data were performed using the Mann-Whitney nonparametric test or the Fisher exact test between patients having acute infusion reactions before and after the recommendations were implemented, and between patients having symptoms of Groups A and B. P values less than 0.05 were considered significant.

RESULTS

Prevalence of infusion reactions. This series of 203 consecutive patients treated with INF included 134 patients with RA and 69 with SpA. We observed 28 (13.8%) infusion reactions to INF, including 23 acute reactions (17 RA and 6 SpA) and 5 delayed reactions (2 RA and 3 SpA) (Tables 1 and 2). In RA and SpA patients, the frequencies of overall reactions were 14.2% and 15.9%, and frequencies of acute reactions were 12.7% and 8.7%, respectively (Table 1). The percentage of infusion reactions was 9.7% of all infusions in patients having an infusion reaction (Table 3).

Acute infusion reactions. Characteristics of patients. Characteristics of RA or SpA patients with acute reactions are given in Table 4. No statistical difference was observed between patients before and after the recommendations were implemented (Table 4). Two RA and 5 SpA patients were taking no immunosuppressive drugs. Fifteen RA patients and one SpA patient were taking prednisone (Table 1).

Eleven patients (9 RA and 2 SpA) had Group A symptoms (increased blood pressure, erythema, sudden flush, or pruritus; Table 2). Two patients (Patients 21 and 23) were not taking any immunosuppressive drugs (Table 1). Twelve patients with

Table 1. Characteristics of patients having infusion reaction to infliximab.

Patient	Age, (yrs)	Sex	Disease	Disease Duration, (yrs)	Treatment	ANA Before Infliximab	ANA Before Infusion Reaction	Type of Infusion Reaction	
								Acute	Delayed
1	69	F	RA	20	MTX + PRED	160	> 1000	•	
2*	65	F	RA	10	LEF + PRED	> 1000	> 1000	•	
3*	60	F	RA	16	MTX	80	> 1000	•	
4	75	F	RA	10	PRED	0	> 1000	•	
5	33	F	RA	18	MTX + PRED	80	300	•	
6	69	F	RA	25	LEF + PRED	ND	> 1000		•
7	61	F	RA	10	PRED	0	0	•	
8	40	F	RA	9	MTX + PRED	0	160		•
9	63	F	RA	8	MTX + PRED	160	0	•	
10	71	M	RA	16	MTX + PRED	0	0	•	
11	35	F	RA	7	MTX + PRED	0	300	•	
12*	59	M	RA	13	MTX + PRED	0	ND	•	
13	63	F	RA	16	MTX + PRED	0	0	•	
14	25	M	RA	11	MTX + PRED	0	> 1000	•	
15*	70	F	RA	5	LEF	160	80	•	
16	70	F	RA	18	MTX + PRED	> 1000	> 1000	•	
17*	38	F	RA	4	MTX + PRED	> 1000	> 1000	•	
18	69	M	RA	7	MTX + PRED	300	> 1000	•	
19*	37	F	RA	19	MTX + PRED	0	> 1000	•	
20	53	F	SpA	3	ø	0	0		•
21	44	M	SpA	15	ø	0	0	•	
22*	35	M	SpA	11	ø	0	80	•	
23*	43	M	SpA	11	ø	> 1000	> 1000	•	
24	59	F	SpA	6	ø	0	0		•
25	48	F	SpA	13	MTX	0	0	•	
26	56	M	SpA	8	ø	80	600	•	
27	35	M	SpA	7	SSZ + PRED	0	0	•	
28	40	F	SpA	7	MTX	80	160		•

RA: rheumatoid arthritis; SpA: spondyloarthritis; MTX: methotrexate; PRED: prednisone; LEF: leflunomide; SSZ: sulfasalazine; ANA: antinuclear antibodies; ND: not determined; ø: no treatment. * The acute infusion reaction to infliximab occurred before the application of the recommendations.

RA (n = 8) or SpA (n = 4) had a severe acute infusion reaction with Group B symptoms (throat irritation, Quincke's edema, dyspnea, vagal malaise with urticaria). Five patients (Patients 4, 7, 22, 26, and 27) were not taking immunosuppressive drugs (Table 2). In each disease, no statistically significant difference was observed between patients belonging to Group A versus Group B in terms of age, disease duration, sex ratio, morning stiffness, tender joint count, patient's assessment of disease activity, treatments, ESR, CRP, latex or Waaler-Rose result, or ANA, with the exception of swollen joint count, patient's assessment of pain, and DAS28 (Table 5).

Some patients presented clinical manifestations of both groups (n = 5). The procedure for these patients was to use the recommendations for Group B symptoms.

In both groups, infusion reactions usually occurred during the sixth or seventh infusion and not during the first one, contrary to our expectations (Table 2).

Validation of the procedure. Before introduction of the procedure described above, INF treatment was immediately stopped for 8 patients having symptoms of Group A (n = 3) or Group B (n = 5) even though it was effective. With this new protocol described above, we maintained the INF treatment for all patients, except one whose INF was stopped completely. In October 2005, INF was continued in 6/15 patients, while it was discontinued in 9/15 patients because of a new acute infusion reaction (n = 1), treatment failure (n = 5), dropouts (n = 2), and drug effects (n = 1). Outcomes of other patients who had acute infusion reactions are given in Table 3.

Acute reactions with Group A clinical symptoms. Eight patients developed Group A symptoms. In 6 patients with increased blood pressure, we reduced the infusion flow to 80 ml/h. In Patient 9, whose blood pressure increased to 190/90 and 170/90 mm Hg during the seventh and eighth infusions, respectively, we reduced the flow to 80 ml/h, which resulted in blood pressure of 150/90 mm Hg. Patient 5, who had a history of hypertension treated with amlodipine, presented blood pressure of 250/130 mm Hg during the 16th and 17th infusions that required treatment with nicardipine. One tablet of amlodipine and a reduction of the infusion rate to 80 ml/h were prescribed for this patient prior to the 18th and 19th infusions. Nevertheless, the blood pressure remained stable. For the 20th infusion, we only reduced the flow rate, and the blood pressure remained at 140/100 mm Hg. With this approach based on a lower infusion rate, we were able to maintain INF

Table 2. Clinical manifestations of patients with acute infusion reactions to infliximab.

Patient	Timing of Infusion Reaction**	Kind of Infusion Reaction, Group A/B	Clinical Manifestations											
			Group A							Group B				
			BP	P	SF	NV	TB	LM	SF	TI/LE	QE	U	D	DIS
1	6	A	•											
3*	9	A	•		•	•								
5	16	A	•											
9	5	A	•											
10	4	A	•	•	•	•		•						
13	3	A	•											
15*	2	A	•		•			•	•					
16	6	A	•				•							
18	6	A		•	•									
21	5	A	•											
23*	11	A	•		•	•	•							
2*	9	B	•		•					•				
4	6	B								•		•		
7	6	B										•		
11	5	B								•				
12*	8	B			•			•	•			•	•	•
14	6	B										•	•	
17*	5	B	•		•		•			•				
19*	8	B										•	•	
22*	10	B									•			
25	3	B			•					•			•	
26	4	B								•		•	•	
27	5	B	•											•

BP: blood pressure; P: pruritus; SF: sudden flush; NV: nausea/vomiting; TB: tachycardia or bradycardia; LM: lumbar pain/myalgia; SF: shivers/fever; TI/LE: throat irritation/labial edema; QE: Quincke's edema; U: urticaria; D: dyspnea; DIS: distress. * The acute infusion reaction to infliximab occurred before the application of the recommendations. ** i.e., 6th infusion, etc.

Table 3. Number of acute infusion reactions among patients who had a reaction to infliximab and their outcome, before and after application of the recommendations.

	RA, n = 17		SpA, n = 6	
	Before	After	Before	After
No. of infusions	38	260	14	53
No. of acute infusion reactions (%)	6 (15.8)	11 (4.2)	2 (14.3)	4 (7.5)
Type of acute infusion reaction				
Group A	2/6	7/11	1/2	1/4
Group B	4/6	4/11	1/2	3/4
Outcome of patients after infusion reaction				
New infusion reaction	NA	0	NA	1
Infliximab inefficacy	NA	4	NA	1
Withdrawn	NA	1	NA	1
Drug effects	NA	0	NA	1
Continuation of treatment	NA	6	NA	0

NA: not applicable. RA: rheumatoid arthritis; SpA: spondyloarthritis.

treatment during the following infusions (n = 7); no alteration in blood pressure was observed. Pruritus was observed in 2 patients (Patients 10 and 18) during the fourth and sixth infusions, respectively. For these patients, we decreased the infusion rate to 80 ml/h or 60 ml/h, and anti-H1 was given 2 days before and 3 days after the infusion. For every patient, INF was maintained with no further cutaneous manifestations.

Acute reactions with Group B clinical symptoms. For 7 patients (Patients 4, 7, 11, 14, 25, 26, 27), we stopped the infusion and administered IV dexchlorpheniramine and/or methylprednisolone 1 mg/kg. Once the symptoms had disappeared, the infusion was resumed at 60 ml/h. For the subsequent infusions, premedication with anti-H1 was prescribed; this allowed us to maintain the INF therapy. Urticaria observed in 6 patients (Patients 4, 7, 12, 14, 19, 26) simply resolved with slowing the infusion rate.

Delayed reactions. Five patients (2 RA, 3 SpA) experienced delayed reactions as follows: pruritus, Patient 6; drug erup-

Table 4. Clinical and biological characteristics of patients with infusion reaction to infliximab before (n = 8) and after application of recommendations (n = 20).

	RA, n = 19		SpA, n = 9	
	Before (n = 6)	After (n = 13)	Before (n = 2)	After (n = 7)
Sex ratio (M/F)	1/5	2/11	2/0	3/4
Age, yrs	52.8 ± 13.3	55.1 ± 16.7	37.5 ± 4.5	48 ± 8
Disease duration, yrs	9.5 ± 4.2	13.1 ± 5.6	8.5 ± 1.5	9.8 ± 6.1
Morning stiffness, min	81.7 ± 54.3	113.8 ± 64.3	180 ± 0	49.3 ± 13.2
Tender joint count, 0–28	10.2 ± 7.4	13.6 ± 8.1	0	8.3 ± 6.6
Swollen joint count, 0–28	14.8 ± 5.1	13.8 ± 6.8	0	4.6 ± 4.9
Patient's assessment of pain, 0–100	64.2 ± 21.8	52.5 ± 18.3	73.2 ± 18.1	63.6 ± 24.1
Patient's assessment of disease activity, 0–100	65 ± 5	63.6 ± 16.9	82.5 ± 2.5	61.4 ± 23.5
DAS28	5.5 ± 1.1	6.04 ± 1	NA	NA
ESR, mm/h	35.5 ± 29	32 ± 20.5	30 ± 8	18.1 ± 11.4
CRP, mg/l	43.7 ± 31.3	34.8 ± 35.4	12 ± 1	17.4 ± 15.2
Latex test, UI/l	114.8 ± 65.2	163 ± 197	NA	NA
Waaler-Rose test, UI/l	28 ± 18.3	146.5 ± 264.01	NA	NA
Patients with positive ANA, %	66.7	38.5	50	28.6
Drug treatments				
Prednisone, mg/day	12.6 ± 13	12.3 ± 6.6	NA	NA
MTX, mg/wk	12.5 ± 6.1	12.7 ± 7.2	NA	NA
Leflunomide, mg/day	20	20	NA	NA

Except where indicated otherwise, values are mean ± SD. NA: not applicable; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; MTX: methotrexate; ANA: antinuclear antibodies; RA: rheumatoid arthritis; SpA: spondyloarthritis.

Table 5. Comparison of clinical and biological indicators in patients who had acute infusion reaction to infliximab, according to the 2 groups of symptoms.

	RA, n = 17		SpA, n = 6	
	Group A (n = 9)	Group B (n = 8)	Group A (n = 2)	Group B (n = 4)
Sex ratio (M/F)	2/7	1/7	2/0	3/1
Age, yrs	61.5 ± 11.6	47.7 ± 16.4	43 ± 1	43.2 ± 9.4
Disease duration, yrs	13.6 ± 4.9	9 ± 3.4	16.5 ± 6.5	8.7 ± 2.5
Morning stiffness, min	93.3 ± 55.2	88.7 ± 51.3	112.5 ± 67.5	82.5 ± 57.6
Tender joint count, 0–28	13.2 ± 7.7	12.7 ± 8.9	NA	NA
Swollen joint count, 0–28	17.5 ± 5.8	11.1 ± 5.1†	NA	NA
Patient's assessment of pain, 0–100	41.3 ± 11.8	71 ± 17.8†	60	58.7 ± 26.7
Patient's assessment of disease activity, 0–100	62.2 ± 14.9	69.7 ± 19.9	67.5 ± 17.5	62.5 ± 28.6
DAS28	6.39 ± 0.77	5.2 ± 1†	NA	NA
ESR, mm/h	40.3 ± 20.3	22.7 ± 25.25	27.5 ± 10.5	22.7 ± 12.5
CRP, mg/l	48.1 ± 37.8	31 ± 30.2	9 ± 4	17.7 ± 9.9
Latex test, UI/l	182.9 ± 151.3	131.7 ± 194.6	NA	NA
Waaler-Rose test, UI/l	171.5 ± 305.7	60 ± 83.4	NA	NA
Patients with positive ANA before treatment, %	78	25	50	25
Patients with positive ANA before infusion reaction, %	66	86	50	50
Drug treatment				
Prednisone, mg/day	11 ± 7	13.8 ± 11.3	NA	NA
Receiving MTX, mg/wk	14.1 ± 4.6	10.7 ± 8.8	NA	NA
Receiving LEF, mg/day	20	20	NA	NA

Except where indicated otherwise, values are mean ± SD. † Statistical difference between Group A and Group B. NA: not applicable; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; MTX: methotrexate; LEF: leflunomide; ANA: antinuclear antibodies; RA: rheumatoid arthritis; SpA: spondyloarthritis.

tion, Patient 28; nausea with headache and dysphonia, Patient 8; face and larynx irritation, Patient 24; and arthralgia, throat irritation, and fever, Patient 20. We stopped the INF treatment in 2 patients (Patients 8 and 28) because of inefficacy. After the first and second infusions, Patient 20 developed severe clinical manifestations (fever of 39°C, shivering and joint

swelling associated with CRP of 364 mg/ml), leading to INF discontinuation. For the remaining patients, INF treatment was maintained with premedication with anti-H1 and reduction of flow rate to 80 or 60 ml/h, with no delayed reactions.

DISCUSSION

In this prospective study, we determined the prevalence of infusion reactions to INF and developed recommendations for their management. In our population of patients with RA, we observed 11.3% of acute reactions. This type of prevalence is in agreement with the study by Wasserman, *et al* (8.8% of acute infusion reactions)[3]. In Maini *et al*, 16% to 20% of 340 patients receiving INF developed these reactions, leading to discontinuation in 2 cases (one urticaria and one dyspnea)[2]. Side effects related to infusion reactions were mild (headache, nausea) and were controlled by slowing the infusion rate or by prophylactic use of antihistamines or both. However, no reactions were considered to be severe[2].

When confronted with infusion reactions in the early years of biologic therapy, we immediately stopped the treatment, whatever the symptoms. Despite a risk of Quincke's edema with anaphylactoid shock, this approach was probably excessive, because INF therapy was effective for most patients and no alternative (e.g., etanercept or adalimumab) was available in France at that time. However, to our knowledge, no recommendations had been provided for monitoring infusion reactions in patients with RA and SpA, and we were prompted to evaluate local alternatives for improved management of infusion reactions. We have attempted to establish pragmatic recommendations by focusing on (1) the type and severity of reactions; (2) a procedure based on successive steps, first relying on the nurse who is initially confronted with an acute reaction in a patient; and (3) modulation of the infusion rate, which is easy to control. Such a classification based on the type and severity of symptoms appeared to be practical. Indeed, since the nurse is the first to be confronted with an infusion reaction, we focused our approach on availability of procedures for well defined symptoms easily recognized by nursing staff. Moreover, we classified symptoms into 2 groups according to potential severity.

Modulation of the infusion rate is critical for management of all types of symptoms. A decreased flow of infusion is sufficient to control symptoms in Group A, which included hypertension, pruritus, erythema and/or sudden flush, nausea and/or vomiting, lumbar pain and/or myalgia, shivers and/or fever. Moreover, in addition to premedication with anti-H1, modulation of the infusion rate can avoid recurrence of Group B symptoms including throat irritation of the larynx and/or labial edema, Quincke's edema, urticaria, dyspnea, hypotension, and distress. Before introduction of this procedure, treatment was discontinued in 8 cases. By following the procedure, however, we had to stop the infusion completely in only a single patient who developed Quincke's edema. In the other 7 patients, we stopped the infusion until symptoms were alleviated, and then maintained infusion at a rate of 80 ml/h. Following this procedure, all patients except one (who experienced another acute reaction) have continued their treatment with no further reaction (Table 2).

In contrast to the regimen used for rheumatic diseases, gastroenterologists have prescribed 3 infusions for refractory Crohn's disease, with retreatment when a new flare occurs. The risk of developing infusion reactions increases with retreatment. However, some authors have proposed a protocol where the infusion reaction is monitored along with a progressive increase of the flow rate up to 120 ml/h[1,9]. When a reaction occurred, they stopped or reduced the infusion rate, prescribed acetaminophen and diphenhydramine, and restarted the infusion with the same procedure as described above[1,9]. For subsequent infusions, they increased the infusion rate up to 250 ml/h every 15 minutes[1,9]. This approach is very important, because INF was used in retreatment. For patients with rheumatic diseases, INF is a longterm treatment and infusion is generally associated with use of an immunosuppressive drug to reduce the risk of reactions. We chose to start INF at a maximum rate (120 ml/h) as stated in our recommendations, which allowed us to reduce the flow when confronted with moderate symptoms or to stop infusion in the case of severe reactions. Infusion was readministered at a lower rate when the clinical manifestations of the reaction had been alleviated.

In the Trust study bethamethasone pretreatment did not decrease the incidence and severity of infusion reaction[10]. In the study from Farell, *et al*, infusion reactions occurred in spite of premedication with IV hydrocortisone[11]. We observed that most patients (16/23) had previously received corticosteroids for treatment of their chronic disease. In our experience, anti-H1 medications were more effective than corticosteroids to alleviate cutaneous rash. Corticosteroids were only indicated in cases of Quincke's edema and anaphylactoid shock including hypotension. Thus, the effectiveness of corticosteroids for prevention of infusion reactions appears to be minor.

Management of infusion reactions might now be considered an outdated concern since other anti-TNF-α drugs are currently available. For many reasons (i.e., the comfort of the patient who prefers IV administration, potential lack of compliance in some patients who receive drugs prescribed to outpatients, potential anticoagulant treatment that makes repetitive subcutaneous injections difficult, or the need to switch from etanercept or adalimumab to INF in cases of ineffective results or intolerance with these 2 drugs) a high level of interest has been maintained in INF infusion for treatment of RA or SpA.

The physiopathology of infusion reactions remains elusive. The mechanism does not seem to be an acute IgE-mediated hypersensitivity (even though some symptoms and signs observed in acute infusion reactions have been considered anaphylactoid manifestations), since we observed reactions during the first infusion in the absence of any previous antigen

exposure. As well, stopping and restarting INF does not produce a risk of greater toxicity[4]. Moreover, in type 1 hypersensitivity, reintroduction of the allergen immediately induces a reaction, whatever the amount of allergen. However, when a patient developed an infusion reaction to INF, the treatment was still administered and only the flow rate was reduced. Moreover, as in our study, Cheifetz, *et al* did not observe wheezing on chest auscultation, which is a specific sign of allergic hypersensitivity[9]. In addition, these authors measured the serum tryptase concentration (which is elevated after IgE-mediated acute hypersensitivity reactions) and the IgE levels in 11 patients who had an infusion reaction to INF for treatment of Crohn's disease — the serum tryptase and IgE concentrations were normal[9]. So type I IgE-mediated immune reactions seem to be very rare. Finally, INF infusion induces human antichimeric antibodies (HACA), found in 8% of patients with RA who are receiving INF. HACA would increase the risk of infusion reactions[12].

This procedure, using a lower rate of infusion, should only be applied to a patient having an infusion reaction to INF. Since INF infusion reactions affect a minority of patients, it does not exclude the feasibility of 1-hour INF infusion for the majority of patients, as suggested by van Vollenhoven, *et al*[13].

The procedure we describe was mainly based on modulation of the infusion rate, and allowed us to maintain treatment with no further acute infusion reactions in patients with RA and SpA treated with INF. Moreover, reducing the infusion rate can be useful when a patient is at high risk of developing an infusion reaction. Our recommendations permit sustained use of INF so patients may continue to benefit from this therapy.

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