Comparison of the clinical characteristics of vasculitis occurring during anti-tumor necrosis factor treatment or not in rheumatoid arthritis patients. A systematic review of 2707 patients, 18 vasculitis

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Received on December 29, 2006; accepted in revised form on October 2, 2007.

Clin Exp Rheumatol 2008; 26 (Suppl. 49): S23-S29.

Key words: Anti-TNF, rheumatoid arthritis, vasculitis, retrospective.

Competing interests: none declared.

ABSTRACT

Objective. *Comparison of vasculitis occurring in rheumatoid arthritis (RA) patients undergoing anti-tumor necrosis factor (TNF) treatment and those not.*

Methods. *Systematic, retrospective, observational study of all RA patients in one center (1997 - 2004). Vasculitis cumulative incidence in RA patients was calculated in patients receiving anti-TNF or those not. Clinical characteristics of RA and vasculitis were collected. Begaud's imputability tables were used to evaluate the role of anti-TNF in inducing vasculitis.*

Results. *Out of 2707 RA patients, 440 received an anti-TNF. A vasculitis occurred in 6 patients treated with anti-TNF (cumulative incidence: 1.3%), and in 12 patients treated without anti-TNF (cumulative incidence: 0.5%). Characteristics of patients not treated with anti-TNF or treated were respectively (mean): age (years) at vasculitis occurrence: 66.5 vs. 55.3, disease duration (years): 12.2 vs. 13.8, extra-articular features before vasculitis: 16% vs. 60%, number of previous DMARDs: 3.2 vs. 4.5, corticosteroid cumulated dosage (grams): 40.8 vs. 64.3. Vasculitis was cutaneous (58% vs. 67%), neurologic (58% vs. 67%), visceral (8% vs. 17%), and required a treatment in 66% vs. 83%. Using Begaud's tables, anti-TNF could be responsible for inducing vasculitis in 2 out of 6 patients.*

Conclusion. *In RA, vasculitis is more frequent during anti-TNF treatment than without anti-TNF. Anti-TNF could be responsible for inducing vasculitis in 2 patients. Patients treated with anti-TNF had more severe RA. It remains to be determined whether vasculitis is a consequence of anti-TNF inefficacy or whether it is treatment-related. In vasculitis occurring with anti-TNF, classical treatment seems more suitable than a switch to another anti-TNF.*

Introduction

Vasculitis is a rare complication of rheumatoid arthritis (RA) usually occurring in severe RA patients (1). Anti-tumor necrosis factor (TNF) drugs (infliximab, etanercept, adalimumab) are often prescribed to severe RA patients who respond poorly to disease modifying anti-rheumatic drugs (DMARDs) and anti-TNF have also been proposed in RA-associated vasculitis with efficacy in several refractory case reports (6, 7). On the other hand, case reports of anti-TNF induced vasculitis have been published (8-15). Nevertheless, to our knowledge, no study has compared the characteristics of vasculitis occurring in RA patients with and without anti-TNF treatment. This could help to better understand the possible responsibility of anti-TNF in inducing vasculitis in RA patients.

The objective of this study was to compare the clinical characteristics of vasculitis occurring during anti-TNF treatment or not, in RA patients from a single center.

Methods

Study design

A monocenter, systematic, retrospective, observational study was conducted in the rheumatology department of a tertiary referral centre. In-patients and out-patients were selected through a computer survey of patient files from December 1997 to December 2004, with the key words: rheumatoid arthritis, vasculitis. Two groups were retrospectively constituted: RA patients treated with anti-TNF and RA patients never treated with anti-TNF. Patients in whom a vasculitis occurred between December 1997 and December 2004 were selected in both groups. Descriptive data were reported, comparing the clinical characteristics of RA and

vasculitis in the two groups. Because of the heterogeneity of retrospective data collection, immunological data (anti-DNA, ANCA…) were only used to exclude another vasculitis and were not analyzed. Begaud's imputability tables (16) were used to evaluate the responsibility of anti-TNF in inducing vasculitis. These tables are based on chronological data: "challenge" (side effect at the initiation of the drug), "dechallenge" (disappearance of the side effect after discontinuation of the drug), "rechallenge" phenomenon (reoccurrence of the side effect at the reinitiation of the drug) and semiological data (semiology *per se*, alternative non drug related explanation, specific laboratory tests). Using these tables, the drug effect relation can be "very likely", likely", "possible", "dubious" or "excluded".

Patients

Patients were included if they met the American College of Rheumatology criteria for RA (17) and vasculitis was considered if the Scott and Bacon vasculitis criteria were satisfied (18). The presence of one or more of the following features in RA patients was required: mononeuritis multiplex or acute peripheral neuropathy, nail fold infarcts, biopsy evidence of acute necrotising arteritis plus systemic illness (*e.g.*, fever, weight loss), deep cutaneous ulcers, active extra-articular disease if associated with typical nail fold infarcts or biopsy evidence of vasculitis. Patients with other systemic vasculitis at diagnosis were excluded. If a vasculitis occurred before anti-TNF treatment, it was analysed in the group of vasculitis occurring with no anti-TNF treatment. Figure 1 shows the patient selection process.

Data collection

The number of RA patients treated with anti-TNF and not, and the number of patients in whom a vasculitis occurred in each treatment group were collected. The cumulative incidence of vasculitis (defined as the number of RA patients in whom a vasculitis occurred between December 1997 and December 2004, divided by the number of RA patients in the same period) in the two groups was calculated. Patient characteristics were collected: age at initiation of anti-TNF, sex, disease duration at the occurrence of vasculitis, RA clinical aspects, disease activity at the initiation of anti-TNF and at the occurrence of vasculitis by the Disease Activity Score 28 (DAS28) (19), based on the number of swollen joints and painful joints, erythrocyte sedimentation rate, and patient's global health assessment. Rheumatoid factor (RF) positivity at any time during follow-up was recorded as well as the presence of bone erosions (yes/no). Medication data collected included: in all patients the number of previous DMARDs and cumulated dose of corticosteroids; in patients without anti-TNF treatment the number of DMARDs at occurrence of vasculitis; in the group treated with anti-TNF the type, dosage, duration of anti-TNF treatment, if necessary switched to another anti-TNF, and concomitant treatments during anti-TNF therapy. Vasculitis characteristics collected were: in all patients, clinical features of vasculitis (cutaneous, neurological, visceral or systemic involvement), histological or electromyographic findings when available, treatments prescribed because of the vasculitis (corticosteroid bolus, cyclophosphamide, azathioprine); in the group treated with anti-TNF, the duration between anti-TNF initiation and occurrence of vasculitis, the outcome of clinical features in case of switch for another anti-TNF and after discontinuation of the anti-TNF (cured, deceased, sequelae). Analysis was descriptive.

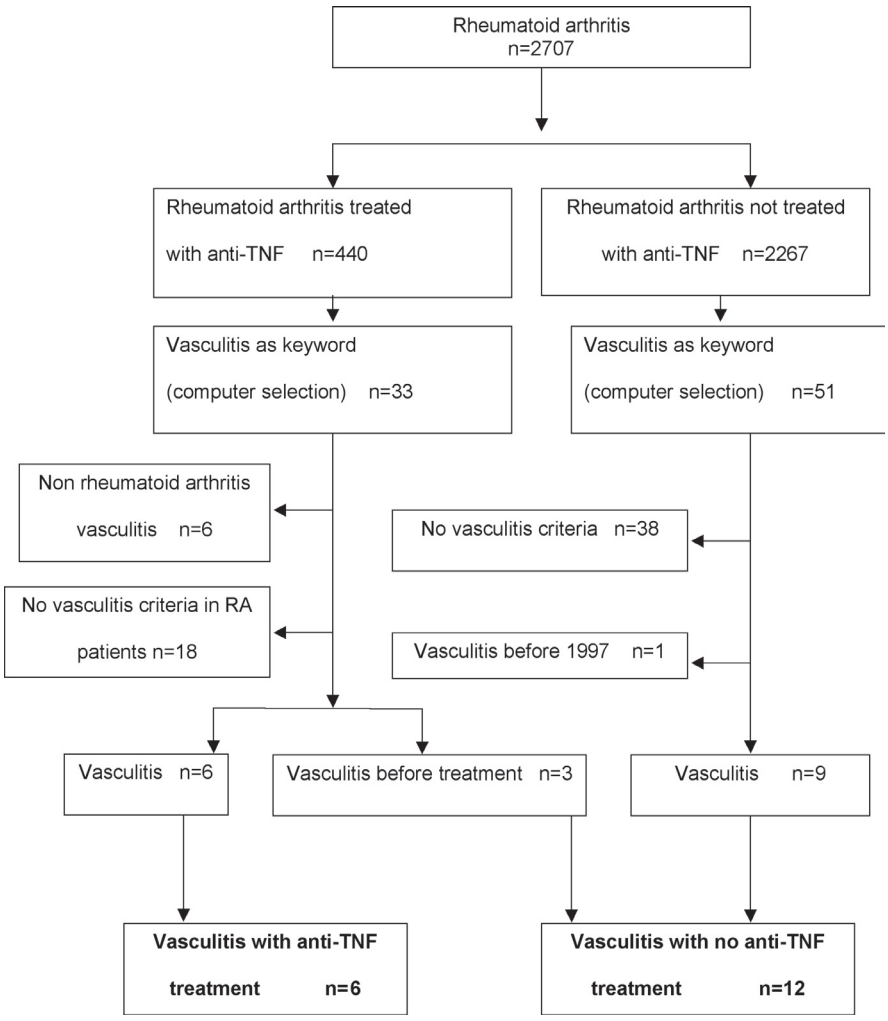

Fig. 1. Flow chart of patient selection. All cases of vasculitis occurring in rheumatoid arthritis patients treated with anti-TNF or not in a rheumatology department, from December 1997 to December 2004.

Table I. Demographic characteristics, clinical features and treatments of rheumatoid arthritis patients with vasculitis with anti-TNF or not.

Patients' characteristics	Vasculitis without prior to anti-TNF treatment n=12	Vasculitis during anti-TNF treatment n=6
Sex, (female), n (%)	10 (83)	5 (83)
Age at occurrence of vasculitis (mean), years	66.5	55.3
Disease duration before vasculitis, (mean), years	12.2	13.8
DAS28 before vasculitis, (mean)	5.7	6.2
Extra-articular features, n (%)	2 (16)	4 (60)
Rheumatoid Factor positivity, n (%)	10 (83)	5 (83)
Bone erosions, n (%)	12 (100)	6 (100)
Number of previous DMARDs (mean)	3.2	4.5
Corticosteroid cumulated dosage (grams), (mean)	40.8	64.3
Vasculitis features:		
Cutaneous, n (%)	7 (58)	4 (67)
Neurologic, n (%)	7 (58)	4 (67)
Visceral involvement, n (%)	1 (8)	1 (17)
Vasculitis treatment, n (%) (cyclophosphamide, azathioprine, corticosteroid bolus)	8 (66)	5 (83)

DMARDs: Disease Modifying Anti-Rheumatic Drugs; DAS 28: disease activity score; Rheumatoid factor positivity: 20 UI (ELISA).

Results

Cumulative incidence of vasculitis

Out of 2707 RA patients, 440 were treated with anti-TNF and 2267 received disease modifying anti-rheumatic drugs (DMARDs) between 1997 and December 2004 (Fig. 1). No patients suffering from a vasculitis received a biotherapy other than anti-TNF. Three patients had a vasculitis before anti-TNF treatment, which was cured with classical vasculitis treatment and did not reoccur during anti-TNF treatment given later in the course of the rheumatoid arthritis disease. These patients were analysed in the group of vasculitis occurring without anti-TNF. During the study period (7 years), vasculitis occurred in 6 RA patients treated with anti-TNF (cumulative incidence: 1.3%), and in 12 RA patients treated with DMARDs (cumulative incidence: 0.5%).

Table II. Characteristics of anti-TNF treatment and concomitant DMARDs in 6 vasculitis occurring in rheumatoid arthritis patients.

Patient	Anti-TNF: Type Duration (weeks)	interval anti-TNF/ vasculitis (weeks)	Concomitant DMARDs	Vasculitis features	Management of anti-TNF	Vasculitis treatment
1	Etanercept 12	12	/	Neurologic Cutaneous	Etanercept interruption Spontaneous regression of the vasculitis. Switch to infliximab 16 weeks after etanercept interruption	none
	Infliximab 90	90	Methotrexate	Neurologic Cutaneous	Reoccurrence of vasculitis. Infliximab interruption	Azathioprine Sequelae of vasculitis
2	Infliximab 32	32	Methotrexate	Neurologic	Infliximab interruption spontaneous disappearance of vasculitis	none
3	Infliximab 75	75	Methotrexate	Cutaneous	Infliximab and methotrexate interruption Immediate switch to etanercept without succes	Azathioprine without success
	Etanercept 14	/	Azathioprine	Cutaneous	Persistence of cutaneous vasculitis. Etanercept and azathioprine interruption	Methyl-prednisolone bolus disappearance of vasculitis
4	Infliximab 12	12	Methotrexate	Cutaneous	Infliximab interruption	Methyl-prednisolone bolus disappearance of vasculitis
	Etanercept 142	/	Methotrexate	none	No reoccurrence of vasculitis	/
5	Etanercept 84	84	Methotrexate	Neurologic	Etanercept interruption Switch to adalimumab 52 weeks after etanercept withdrawal.	Azathioprine with success
	Adalimumab 32	52	Azathioprine	none	No reoccurrence of vasculitis	/
6	Etanercept 52	52	Methotrexate	Systemic Neurologic Cutaneous	Etanercept interruption Immediate switch to Infliximab	none
	Infliximab 2	/	Methotrexate	Systemic Neurologic Cutaneous	Persistence of the vasculitis infliximab withdrawal	Methyl-prednisolone bolus and Cyclo-phosphamide Cutaneous and systemic vasculitis disappearance. Sequelae of neurologic signs

DMARDs: Disease Modifying Anti-Rheumatic Drugs.

Patient and vasculitis characteristics (Tables II and III)

No patient was referred specifically because of vasculitis. Patients with a vasculitis occurring during anti-TNF therapy were younger (55.3 *vs*. 66.5 years), with a longer mean disease duration before vasculitis (13.8 *vs*. 12.2 years), more active disease (DAS28 6.2 *vs*. 5.7), more extra articular features before vasculitis (60% *vs*. 16%), higher mean number of previous DMARDs (4.5 *vs*. 3.2) and higher mean corticosteroid cumulated dosage (64.3 *vs*. 40.7g). The proportion of cutaneous, neurologic and visceral vasculitis was higher in the group treated with anti-TNF (67 *vs*. 58% for cutaneous and neurologic features, and 17 *vs*. 8% for visceral involvement). All cutaneous vasculitis were purpuric lesions of the limbs, and only one had a cutaneous biopsy, which showed a vasculitis without palissadic extra vessel granuloma. All neurologic vasculitis consisted of feet paresthesia, one had an electromyographic proof. More patients required a specific treatment for vasculitis in the group treated with anti-TNF (83 *vs*. 66%). At the occurrence of vasculitis in patients not treated with anti-TNF, the number of concomitant DMARDs per patient was: 0 (n=1), 1 (n=7), 2 (n=3) or 3 (n=1), mean=1.3. In the group treated with anti-TNF (Table I), all vasculitis appeared with infliximab (n=3) or etanercept (n=3) after a mean duration of 39.7 and 49.3 weeks respectively. The anti-TNF was not efficacious in treating RA symptoms at the occurrence of the vasculitis, as evaluated by disease activity (mean DAS28 at occurrence of vasculitis was 5.6 *vs*. 6.1 at initiation of anti-TNF), except in one case where the RA disease was in remission (DAS28: 2.4 at occurrence of vasculitis *vs*. 5.1 before anti-TNF treatment).

Treatment and resolution of vasculitis (Table II)

The first patient received etanercept and developed after 12 weeks of use a vasculitis with neurologic (feet paresthesia) and cutaneous (purpuric lesions of the lower limbs) signs. Etanercept was interrupted and a spontaneous regression of the vasculitis signs occurred. Because of RA flare 90 weeks later, without vasculitis signs, infliximab was introduced. The neurologic and cutaneous signs of vasculitis reoccurred, and infliximab was interrupted while azathioprine was introduced. Cutaneous signs disappeared, and sequelae of neurological vasculitis remained.

The second patient received infliximab which was interrupted at occurrence of a neurologic vasculitis (symmetrical lower limb parethesia) after 12 weeks of use. The vasculitis symptoms disappeared spontaneously without sequel in one month. At the occurrence of the vasculitis signs the patient was in remission of rheumatologic symptoms.

The third patient received infliximab for 75 weeks before developing a purpura of the lower limbs which was consistent with a cutaneous vasculitis. Infliximab was stopped and etanercept and azathioprine introduced without success. The vasculitis resolved only after etanercept discontinuation associated with methylprednisolone bolus.

The fourth patient developed a cutaneous vasculitis (symmetrical purpuric lesions of the lower limbs) 12 month after infliximab introduction. Infliximab was immediately switched to etanercept associated with methylprednisolone bolus. Cutaneous signs disappeared although etanercept was maintained.

The fifth patient received etanercept for

Table III. ANNEX: Immunological data (before and after anti-TNF-α treatment) in 6 rheumatoid arthritis patients with a vasculitis appearing during anti-TNF-α treatment.

Patients	IMMUNOLOGY before anti-TNF-α	IMMUNOLOGY during vasculitis signs.
1	RF positive ANA negative Native anti DNA negative Complement normal Proteiruria negative	RF positive ANA 1/320 U/ml, Native anti DNA 47 U/ml, ANCA 160 U/ml, Cryoglobulinemia negative Complement normal Proteinuria negative
2	RF positive ANA negative Native anti DNA negative Complement normal Proteiruria negative	none
3	RF negative ANA 1/640 U/ml Native anti DNA negative	RF positive ANA 1/640 U/ml Native anti DNA negative ANCA negative Cryoglobulinemia negative Complement normal Proteiruria 0.39/24h
4	RF positive ANA negative ANCA positive 1/160 U/ml Complement normal Proteinuria 0.37g/24h	RF positive ANA negative Native anti DNA negative Cryoglobulinemia negative Complement normal Proteiruria negative
5	RF positive ANA 1/80 U/ml	RF positive ANA 1/80 U/ml
6	RF positive ANA negative	RF positive ANA 1/80 U/ml Native anti DNA negative ANCA negative Cryoglobulinemia negative

RF: rheumatoid factor, U/ml (ELISA normal value<10 U/ml); ANA: antinuclear antibody (indirect immunofluorescence), u/ml, (normal value <1/80 U/ml); Native anti DNA with ELISA normal value <20 u/ml; ANCA (indirect immunofluorescence), with no specificity.

84 weeks and developed paresthesia of the lower limbs. Etanercept was interrupted while azathoprine was introduced. A regression of the vasculitis signs occurred. Because of RA flare 52 weeks later, without vasculitis signs, adalimumab was introduced without the reoccurrence vasculitis.

The last patient received etanercept for 52 weeks and developed purpuric lesions of the limbs, feet paresthesia, fever, weight loss, pleural fluid. Skin biopsy confirmed the diagnosis of vasculitis and electromyography showed a sensitive and motor axonal neuropathy. Etanercept was immediately switched to infliximab (2 infusions) but the patient worsened and infliximab was stopped; methylprednisolone bolus and cyclophosphamide infusions were efficacious on systemic and cutaneous signs, with stabilization and persistence of neurological signs (considered as sequelae).

Five patients were switched to another anti-TNF at occurrence of vasculitis (Fig. 2): etanercept to infliximab (n=2), infliximab to etanercept (n=2), etanercept to adalimumab (n=1). The second anti-TNF was introduced immediately in 3 patients and later in 2 patients (respectively 16 and 52 weeks later). After discontinuation of the first anti-TNF, vasculitis spontaneously disappeared in 2 patients, without treatment, in one month.

After the second anti-TNF introduction, a reoccurrence (n=1) within a month (positive rechallenge phenomenon) or a persistence (n=2) of vasculitis with the same clinical features was observed in 3 of 5 patients (despite the use of another anti-TNF). Vasculitis did not reoccur in 2 patients in whom the anti-TNF was switched and maintained, but in both cases another treatment to cure the vasculitis was added (azathioprine or methylprednisolone bolus). It is therefore difficult to know which treatment was efficacious: anti-TNF switch or classic vasculitis treatment. Considering all patients, interruption of anti-TNF immediately associated to a specific treatment for the vasculitis was required in 5 with total efficacy (n=3) or stabilisation with sequelae (n=2). No death was observed.

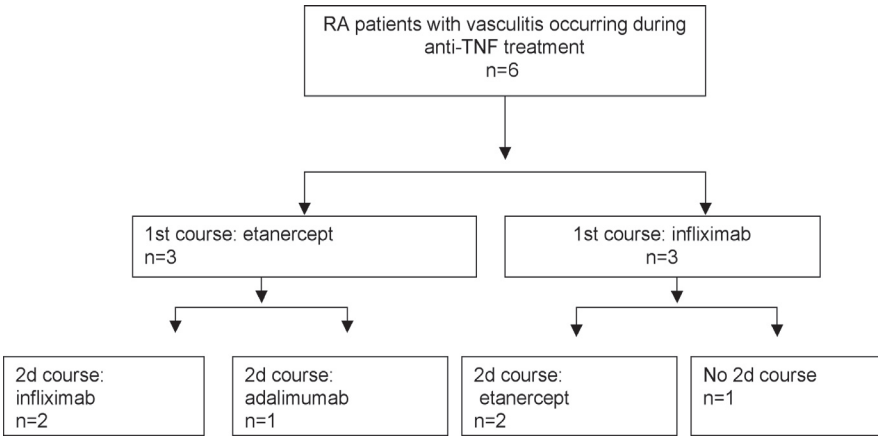

Fig. 2. Flow chart of patient treatments (vasculitis occurring in rheumatoid arthritis patients treated with anti-TNF) from December 1997 to December 2004.

Responsibility of the anti-TNF treatment

Using Begaud's imputability tables (16), anti-TNF could be considered as "possibly" responsible for inducing the vasculitis in 2 patients (patients 1 and 2).

Discussion

In this systematic daily practice study on a large sample of patients, the cumulative incidence of vasculitis occurring over 7 years in RA patients treated with anti-TNF or not was low (respectively 1.3% and 0.5%) and 2.6 times higher with anti-TNF than without. Although both groups suffered from severe long standing RA, patients treated with anti-TNF suffered from more severe RA. Patterns of vasculitis, though similar, differed by their frequency when occurring with or without anti-TNF treatment: visceral forms were more frequent in the group treated with anti-TNF. An immediate classical treatment of the vasculitis was more often required in vasculitis occurring during anti-TNF. Vasculitis could be considered therefore as more severe in patients treated with anti-TNF.

However there is a confounding bias by indication: because vasculitis often occurs in severe RA patients and severe RA is often treated with anti-TNF, it is difficult to know which phenomenon is responsible for vasculitis: evolving disease or treatment. These two hypotheses can be considered. The severity of the underlying disease could be an argument for considering vasculitis as a rheumatoid associated vasculitis flare rather than an adverse event of anti-TNF: it is recognized that severe RA patients are more likely to suffer from vasculitis than mild RA patients. Similar patients characteristics were found in both groups of patients, whatever the use of anti-TNF prior the onset of the vasculitis: these patients had all long standing seropositive destructive RA which is typically the case in systemic vasculitis associated with RA. The clinical characteristics of the patients between the 2 groups may argue in favor of a rheumatoid specific vasculitis not linked with anti-TNF therapy. In patients treated with anti-TNF, 5 out of 6 vasculitis occurred when anti-TNF seemed to be associated with an articular flare, leading to the hypothesis of a rheumatoid-associated vasculitis, because of anti-TNF inefficacy.

Nevertheless, some mechanisms have been put forward in anti-TNF induced vasculitis: the development of native anti-DNA and anti-nuclear anti-bodies during anti-TNF therapy might also be responsible for induced disseminated lupus erythematosus and systemic vasculitis. Deposition in the vessels of anti-TNF/TNF-complexes can trigger type III hyper sensibility reaction, responsible for a switch from the predominant Th1 profile of RA to Th2 response, possibly inducing Th2 lymphocyte mediated vasculitis (11). The chronological criterion is finally the only one to define vasculitis as a potential adverse event of anti-TNF (20). Using Begaud's imputability tables, anti-TNF could be considered as

possibly responsible for inducing the vasculitis in 2 of 6 patients (33%). A positive dechallenge phenomenon was observed in 2 patients (the spontaneous improvement of the clinical signs after a simple discontinuation of the therapy supports the hypothesis of drug induced vasculitis (16)). A positive rechallenge phenomenon was observed in 3 patients with the persistence or reoccurrence of the vasculitis after the second anti-TNF introduction (which represents a strong argument for a drug induced side effect) (Table II). In anti-TNF treated patients, vasculitis was finally cured only after anti-TNF discontinuation and appropriate treatment (nevertheless, it may be difficult to assess which therapy was efficacious: discontinuation of the anti-TNF or specific vasculitis treatment). In another study, similar chronological aspects in vasculitis occurring during anti-TNF treatment were reported: in 35 patients who developed a vasculitis during anti-TNF treatment (etanercept n=20, infliximab n=15), 22 experienced a total or marked regression of skin lesions after anti-TNF withdrawal. In 6 patients, vasculitis reoccurred after restarting anti-TNF therapy (14). Furthermore, in this same study (14), vasculitis occurred during anti-TNF therapy in diseases in which vasculitis is unusual (spondylarthropathies). Although several case reports or small studies describe the possible occurrence of vasculitis during anti-TNF treatment, the role of anti-TNF in inducing vasculitis in RA patients remains uncertain. The present study shows that anti-TNF do not always prevent the onset of vasculitis in RA patients even though anti-TNF therapy has been considered in several case reports as a possible therapeutic option. This study is retrospective, with a small number of vasculitis. The other limitation of this study is the absence of histological proof of the vasculitis. The histology would have been useful to precise the type and mechanism of the vasculitis. The cumulative incidence found in this study (with or without anti-TNF) is lower than the cumulative incidence of RA associated vasculitis previously published (21). Studies of incidence of rheumatoid vasculitis are rare and concern small number of patients. The present study is a large, exhaustive, homogeneous cohort of 2707 patients treated in a single center, and the incidence found could be closer to the real cumulative incidence of vasculitis in RA. To our knowledge, it is also the first study comparing the cumulative incidence of vasculitis during anti-TNF treatment versus without this treatment. Furthermore, it is to date one of the largest studies concerning the occurrence of vasculitis during anti-TNF therapy. This study was performed in clinical practice conditions, and was exhaustive of all patients of the center.

This work should have a direct impact on clinical practice. In case of vasculitis occurring during anti-TNF therapy, and because there is a possibility of anti-TNF induced vasculitis, the recommendation could be to discontinue anti-TNF treatment. A switch for another anti-TNF should be avoided: in the case of anti-TNF induced vasculitis, the switch seems able to induce persistence or reoccurrence of vasculitis. If the vasculitis occurs because of anti-TNF inefficacy, this treatment has no need to be continued. Therefore, the use of classical therapies to cure the vasculitis appears to be to date a more logical approach than a switch to another anti-TNF, and is supported by our data. If the vasculitis is not severe, the isolated anti-TNF discontinuation and a strict follow up, without vasculitis classical therapy introduction can be discussed. In case of persistence of the clinical features or in case of a severity criterion, the classical therapy could be introduced. Because anti-TNF are recent treatments, practitioners have to be aware of new potential drug induced adverse events, among which possible anti-TNF induced vasculitis in some patients. This will become a rising issue with the ever larger use of these drugs. Further studies seem necessary to assess the imputability of anti-TNF in inducing vasculitis in RA patients.

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