Recommendations for the use of biologic therapy in rheumatoid arthritis: update from the Italian Society for Rheumatology

II. Safety

E.G. Favalli¹, R. Caporali², L. Sinigaglia³, N. Pipitone⁴, I. Miniati⁵, C. Montecucco², M. Matucci-Cerinic⁵

1Division of Rheumatology, University of Milan, Istituto Ortopedico G. Pini, Milano, Italy; 2Division of Rheumatology, University of Pavia, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy; 3Department of Rheumatology, Struttura Complessa di Reumatologia DH, Istituto Ortopedico G. Pini, Milano, Italy; 4Department of Rheumatology, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy; 5Department of Biomedicine, Division of Rheumatology, DENOThE Centre, University of Florence, Florence, Italy.

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ABSTRACT

Given the availability of novel biologic agents for the treatment of rheumatoid arthritis (RA), various national scientific societies have developed specific recommendations in order to assist rheumatologists in prescribing these drugs. The Italian Society for Rheumatology (Società Italiana di Reumatologia, SIR) decided to update its recommendations, and, to this end, a systematic literature review was performed and the evidence derived from it was discussed and summarised as expert opinions. Levels of evidence and strength of recommendations were reported. The recommendations reported refer to the safety of biologic agents and are intended to help prescribing rheumatologists to optimise the use of biologic agents in patients with RA seen in everyday practice; they are not to be considered as a regulatory rule.

Introduction

Biologic therapies have had a profound impact on the treatment of patients with rheumatoid arthritis (RA); however, safety concerns have emerged after their use in everyday practice and specific recommendations have been published by different rheumatologic societies in order to minimise possible adverse events.

The Italian Society for Rheumatology (Società Italiana di Reumatologia, SIR) has previously published a set of recommendations for the use of anti-TNF therapies in RA (1), which included safety issues, and now presents an update taking into account data from randomised controlled studies (RCTs) and data coming from large national registries. In this paper we will focus on the safety of biologic treatments, presenting recommendations on the main issues raised from more than 10 years of biologic treatment use in everyday clinical practice (2). The evidence coming from the literature was discussed and summarised as recommendations, with level of evidence, strength of recommendation as well as level of agreement clearly stated.

Autoimmunity

The new appearance of circulating autoantibodies, such as antinuclear (ANA), anti-phospholipid and anti-double-stranded DNA antibodies (anti-dsDNA) is a common finding during the administration of TNF blocking agents (particularly monoclonal antibodies) as reported both in main RCTs, (level of evidence 1B) (3-6)) and in observational studies (level of evidence 2B) (7-12). ANA and anti-dsDNA become positive respectively in up to 40% and 25% of patients treated with infliximab (13) and in up to 12% and 11% of those treated with adalimumab (14). However, related clinical autoimmune syndromes (anti-phospholipid and lupus-like mainly) are rare and reversible after anti-TNF therapy withdrawal (level of evidence 3b and 4) (15-22). No increased incidence of autoimmune diseases was reported in the abatacept clinical trial database (level of evidence 1a) (23). No evidence of autoimmunity during therapy with rituximab and anakinra has been published.

Recommendations

• ANA positivity does not contraindicate treatment with biological agents (grade of recommendation B).
• ANA and anti-dsDNA formation during anti-TNF treatment in the absence of clinical syndromes does not preclude the continuation of the treatment (grade of recommendation B).
• In the case of a new-onset clinical
autoimmune syndrome during anti-TNF treatment, withdrawal of biological agent is recommended (grade of recommendation C).

Injection site/infusion reactions
Injection site reactions (ISRs, consisting of localised erythema, itching, pain or swelling) with subcutaneous TNF blockers in RCTs have been reported to be more common in treated patients (up to 26% of patients with adalimumab and 21% with etanercept) than with placebo, and were generally mild to moderate and only in rare cases resulted in drug discontinuation (level of evidence 1b) (5, 14, 24).

Acute reactions (within 24 hours) with intravenous infliximab are reported with an incidence between 4% and 21% of patients and were generally mild to moderate, even if serious reactions (such as anaphylactoid manifestations) have been reported in rare cases (level of evidence 1b) (13, 25). Occasionally, delayed forms of reaction may occur as a serum sickness-like illness (level of evidence 4) (26). The presence of human anti-chimeric antibodies (HACA) against infliximab may increase the incidence of infusion reactions (level of evidence 3a) (27). Low-dose daily corticosteroids were reported to be associated with a significantly lower risk for a treatment-limiting infusion reaction (level of evidence 2b) (28), whereas intravenous corticosteroids pretreatment may reduce HACA formation (level of evidence 2b) (29), but do not decrease the incidence and severity of infusion reactions (level of evidence 1b) (30). Moreover, shortened infliximab infusion time does not seem to compromise safety if initial infusions are well tolerated (level of evidence 2b) (31). Infliximab infusion reactions may be treated by slowing the infusion rate or by the administration of corticosteroids and/or antihistamines (level of evidence 2b) (32).

Rituximab acute infusion reactions (generally mild to moderate) are common and more frequent after the first infusion of each course (up to 38%, level of evidence 1b) (33, 34). Rarely, delayed serum sickness-like reactions may occur (level of evidence 4) (35).

Infusion reactions can be reduced and managed by premedication with an antihistamine, acetaminophen, and corticosteroids, or by slowing the rate of infusion (level of evidence 1a) (36). Acute infusion reactions with abatacept are uncommon (less than 10% of patients) and mostly mild to moderate in intensity (level of evidence 1b) (37-39). Considering RCTs pooled safety data, less than 1% of patients experienced severe hypersensitivity reactions, including two cases of anaphylaxis or anaphylactoid reactions (level of evidence 1a) (40).

In main RCTs with anakinra, ISRs are the most commonly reported adverse event, occurring in up to 70% of patients (level of evidence 1b) (41, 42). Most ISRs are of mild or moderate severity and are transient in nature, but represent the most common event leading to anakinra withdrawal in clinical practice (level of evidence 2b) (40).

Recommendations
• When a severe infusion reaction occurs with any iv biological agent, infusion must be stopped and treatment with corticosteroids and/or antihistamines should be considered (grade of recommendation B).
• Mild to moderate infusion reactions with any iv biological agent may be treated by slowing infusion rate or by the administration of corticosteroids and/or antihistamines (grade of recommendation B).
• When a severe/moderate infusion reaction is experienced with any iv biological drug, switch to another biological drug, or by slowing the rate of infusion or by the administration of corticosteroids and/or antihistamines (grade of recommendation D).
• Premedication with antihistamines, acetaminophen (paracetamol), and corticosteroids is mandatory before rituximab infusions, whilst it seems ineffective in reducing reaction frequency and severity in infliximab treated patients (grade of recommendation A).

Infections
Tuberculosis
TNF-α is a key cytokine in protecting host defence against Mycobacterium tuberculosis and, together with TNF-dependent chemokines, plays an important role in the development and maintenance of the granuloma (level of evidence 1b) (44, 45). Thus, TNF inhibition can increase the susceptibility to mycobacteria and particularly can promote the reactivation of latent tuberculosis infection (LTBI) in previously exposed patients (46).

Several spontaneous case presentations and observational studies (mainly based on national registries) have reported an increase in active tuberculosis infections (ATBI) associated with the use of TNF antagonists (level of evidence 4) (47-50). The majority of cases occurred shortly after starting anti-TNF therapy, suggesting a reactivation of LTBI; nevertheless, delayed cases consistent with new infection have occasionally been reported (level of evidence 4) (51). Clinical manifestation of anti-TNF-related ATBI may be often atypical, such as miliary or extra-pulmonary presentation (level of evidence 4) (50). Differences among TNF blockers with respect to mechanism of action, pharmacokinetics or biology suggests the possibility of a different risk for granulomatous infections (52). Recent data from observational studies showed a higher risk of ATBI associated with monoclonal antibodies than with etanercept (level of evidence 2b) (53, 54). Nevertheless, in the absence of head-to-head comparisons among anti-TNF agents, an increased susceptibility to ATBI has to be intended as a class effect to date.

A recently published survey highlighted the increasing incidence of non-tuberculous mycobacterial infection (up to 50% Mycobacterium Avium) in TNF blocker treated patients (level of evidence 4) (55). To address concerns about increased susceptibility to ATBI or reactivation of LTBI, screening for tuberculosis must be performed before beginning therapy with anti-TNF agents. In accordance to local guidelines, screening for LTBI should include: a tuberculin skin test (TST, with positive result >5 mm), a chest radiograph (showing evidence of past tuberculosis), and history of prior exposure to ATB or prior partially treated ATB (56, 57).
Because antigens within PPD are also found in other mycobacteria, the TST suffers from poor specificity in bacille Calmette-Guérin (BCG)-vaccinated persons (58). Moreover, the sensitivity of the TST used to diagnose LTBI may be reduced in patients on immunosuppressive therapy with a high rate of false-negative results (59). Since the early 2000s, in vitro blood tests measuring production of interferon (IFN)-γ by T cells exposed to antigens highly specific for Mycobacterium tuberculosis have been developed (60, 61). Extensive published literature suggests that T-cell INF-γ release assays (IGRAs) are a more specific and probably a more sensitive test for diagnosis of M. tuberculosis infection than the TST in immunocompetent persons (62), but available data in population affected by immune-mediated inflammatory diseases treated with conventional immunosuppressants are limited (level of evidence 2b) (63-65). Thus, IGRAs may be a promising tool for screening patients candidate to TNF blockade, but more data are required to validate their specific role in this setting.

Observational studies indicate that pre-treatment with antitubercular drugs in LTBI patients candidate to anti-TNF therapy may significantly reduce, even if not abolish, the risk of reactivation (level of evidence 2b) (66, 67). To date, no prospective controlled trial evaluating the optimal duration of prophylactic treatment and the optimal time frame between its beginning and starting of anti-TNF therapy has been published. Observational data suggest to start anti-tubercular drugs at least one month before starting biologic treatment (level of evidence 2b) (68) and to stop it after a period consistent with local guidelines.

Apart from data collected from a small series of patients (level of evidence 4) (68), no definitive data exist on the utility of repeating TST in previously negative patients during anti-TNF treatment. A history of TB after successful completion of a full course of anti-tuberculous treatment does not contraindicate the start (or re-start) of anti-TNF treatment (level of evidence 2b) (69).

No data have been published on a significantly increased risk of tubercular complication during treatment with rituximab, abatacept, and anakinra.

**Recommendations**

- LTBI screening (TST, chest x-ray and exposure history) is mandatory before starting a treatment with anti-TNF agents (grade of recommendation B).
- Until the real risk is well known, it is appropriate to screen for TB also patients considered for other biologic agents (rituximab and abatacept) according to local guidelines (grade of recommendation D).
- In selected patients (low-grade TST positivity and previous BCG vaccination) IGRAs may be useful to complete the screening program (grade of recommendation C).
- RA patients with a positive screening for LTBI must be treated with antitubercular drugs (e.g. isoniazid 300 mg/day for 9 months) for one month before starting biological treatment (grade of recommendation B).
- Re-screening should be considered only in areas of high TB prevalence (grade of recommendation C).

**Other opportunistic infections**

Data from RCTs with all biologic agents do not indicate an increased rate of opportunistic infections in treated patients as compared with control population (level of evidence 1b) (5, 14, 24, 33, 38, 41, 70, 71). On the other hand, isolated cases of opportunistic infections have been reported in patients treated with anti-TNF with particular reference to macrophage/granuloma dependent infections such as listeriosis (72), coccidiodomycosis (73), and histoplasmosis (74, 75).

**Recommendation**

- Based on isolated reports, particular vigilance is needed for the possible development of opportunistic infections in RA patients treated with biological agents (grade of recommendation D).

**Bacterial infections**

Compared with the general population, patients with RA have an increased risk of infection, which is nearly twice as high as that observed in matched non-RA controls (level of evidence 2b) (76, 77)).

In the main RCTs, the rates of infections in patients treated with anti-TNF have been similar to those reported in the placebo group (level of evidence 1b) (4-6, 13, 14, 24, 78, 79). When considering serious infections separately, with the exception of etanercept RCTs (level of evidence 1b) (6, 24, 78, 80, 81), a trend toward an increased frequency compared to classical DMARDs has been noted regarding monoclonal anti-TNF antibodies (level of evidence 1b) (14, 70, 79), with a significant increase reported only in two studies with high (10 mg/kg) and low (3 mg/kg) dose infliximab (level of evidence 1b) (13, 82) and in one study with adalimumab (level of evidence 1b) (5). These findings are consistent with the results of a meta-analysis published in 2006, that included all RCTs performed with infliximab and adalimumab (level of evidence 1a) (83).

Post-marketing observational studies based on national registries produced conflicting results. Data from the German registry indicate that general and serious infections in patients treated with all TNF blockers are significantly increased as compared to DMARDs treated control group (level of evidence 2b) (84), whereas data from other large registries (level of evidence 2b) (85, 86) report a rate of infections similar to DMARDs treated RA population. The most common sites of infection were the respiratory tract (including pneumonia), skin and soft tissue, and the urinary tract.

RCTs data show a numerically but rarely significantly increased incidence of serious and non-serious bacterial infections associated with the use of abatacept (level of evidence 1b) (39, 87, 88), rituximab (level of evidence 1b) (33, 34), and anakinra (level of evidence 1b) (41, 42). Long-term data from registries and observational studies are needed to more clearly define the risk of serious infections when using biological agents other than anti-TNF.

**Recommendation**

- Patients on biological therapy should be carefully monitored for infectious complications. When a bacterial in-
Viral hepatitis
HBV-positive patients treated with TNF-α blocking agents have experienced raised liver function tests, increase of viral load and in some cases fatal hepatic failure (level of evidence 4) (98-102). No reactivation was reported in several observational studies during TNF-α inhibiting therapy in occult HBV carriers (Hbc Ab positive - HBs Ag negative patients) (level of evidence 2b) (103). In HCV-infected RA patients, several short-term observational studies have shown no worsening or reactivation of viral disease associated with anti-TNF therapy (level of evidence 3b and 4) (102, 104-106). Moreover, in one reported controlled trial, the use of etanercept in association with standard anti-HCV therapy showed a significant improvement in viral load, liver enzymes, and symptoms (level of evidence 1b) (107).

Hepatitis C and fatal hepatitis B reactivation have been reported in patients with non Hodgkin lymphoma (NHL) or other haematological diseases treated with rituximab (level of evidence 4) (108-112). On the other hand, there are several reports on the efficacy of rituximab in the treatment of HCV-related mixed cryoglobulinemia (level of evidence 3a and 4 (113-115)) and recent data have confirmed the safety of this treatment even in patients with concomitant severe liver disease (116). Prophylactic antiviral therapy with lamivudine seems to be useful to prevent hepatitis B reactivation in some patients treated with TNF blocking agents (level of evidence 3) (117-119) and in some descriptive studies in NHL patients treated with rituximab (level of evidence 4) (120, 121).

To date, there are no data about HCV/ HBV infections in patients treated with abatacept or anakinra.

Recommendations
- Hepatitis B and C screening tests must be performed before starting biologic treatments (grade of recommendation C).
- The use of anti-TNF-α drugs in active or non-active HCV infected patients seems to be safe and the prophylactic use of antiretroviral agents is not mandatory. Since the long-term safety of TNF blocking agents and rituximab in this condition is unknown, careful monitoring of liver function tests and viral load is recommended (grade of recommendation D).
- TNF-α blocking agents and rituximab are contraindicated in HBV active carriers and should be used carefully in HBV inactive carriers in association with concomitant prophylactic antiviral therapy with lamivudine (grade of recommendation C).

Vaccinations
The ability of patients with RA to respond effectively to vaccination remains uncertain and it has been suggested that treatment with biologics may interfere with the effectiveness of vaccination in these patients. The antibody response to pneumococcal (122-126), influenza (127-130), and measles-mumps-rubella (MMR) vaccine in patients treated with anti-TNF, especially in combination with methotrexate, is reported to be only modestly impaired, but the proportion of patients that achieves a protective titre is not significantly diminished by the use of TNF blocking therapies (level of evidence 3b and 4) (129, 131). Administration of the influenza vaccine on the day of infusion of infliximab seems to produce a better humoral response than vaccination 3 weeks later and may be thus preferable (level of evidence 3b) (132).

Rituximab reduces humoral responses following influenza and polysaccharide pneumococcal vaccination, but treatment with rituximab does not preclude administration of the vaccine (level of evidence 3b) (133, 134). Abatacept reduces the effectiveness of the immune response to tetanus or pneumococcal vaccine, but does not significantly inhibit the ability of healthy subjects to develop a clinically significant or positive immune response (level of evidence 2b) (135). There are no data on vaccination during treatment with anakinra.

Recommendations
- Influenza and pneumococcal vaccination, which can be indicated in RA, can also be safely recommended.
for patients treated with anti-TNF, rituximab or abatacept (grade of recommendation B).

- In the absence of available data, the use of live attenuated vaccines (e.g. BCG, yellow fever, herpes zoster) is not recommended (grade of recommendation D).

### Lymphomas and solid tumours

RA is a well-established risk factor for malignancies (especially lymphomas), but the role of biological and conventional DMARDs is still under debate. A meta-analysis of main RCTs showed a three-fold increase of short-term (less than one year) occurrence of any malignancy with anti-TNF monoclonal antibodies (level of evidence 1a) (83), but not with etanercept (level of evidence 1b) (136). However, data from several large observational studies found no increase in the overall risk of any cancer related to anti-TNF therapy (level of evidence 2b and 3b) (137-139). The risk of lymphoma is increased from two to five-fold in RA patients as compared to control population (140) and this increase appears to be related to disease activity and severity (141). So far, no individual clinical trial has reported an increased risk of developing lymphomas in patients exposed to TNF-α inhibitors, but none has been adequately powered to address this issue (level of evidence 1b) (5, 13, 25, 78, 142, 143). Data from observational studies are inconclusive (level of evidence 2b and 3b) (138, 139), but two large registries stated that TNF-α inhibitors seem to be not associated with an increased risk of developing lymphomas (level of evidence 2b (144, 145)).

The occurrence of solid malignancies with anti-TNF is not increased in RCTs (level of evidence 1b) and in long-term observational studies (level of evidence 2b) (137-139, 146), with the exception of an increased risk (OR: 1.5) (1.2-1.8) of non melanoma skin cancers (level of evidence 2b) (137, 146).

Data from RCTs showed no evidence that rituximab (level of evidence 1b) (33, 34), abatacept (level of evidence 1a) (40) and anakinra (level of evidence 1b) (41-43) are associated with an increased risk of any malignancy, but data from long-term registries are needed to definitely settle this issue.

### Recommendations

- In patients undergoing biological treatment for RA an accurate medical and family history should be taken to assess the risk of developing solid or haematopoietic malignancies (grade of recommendation C).
- Considering the timing of oncologic remission of 5 years, TNF inhibitors should be avoided in patients with a recent history of malignancy (<5 years) (grade of recommendation D).

### Haematological disorders

Haematological dyscrasias such as aplastic anaemia, pancytopenia and neutropenia have been described in patients treated with TNF-α antagonists (level of evidence 4) (19, 147-152). These complications are extremely rare, and causality is very difficult, if not impossible, to ascertain.

No data on haematological dyscrasias during abatacept, anakinra, and rituximab treatment have been published.

### Recommendation

If a patient develops any haematological dyscrasias while on anti-TNF therapy, the agent must be stopped and the patient should be evaluated for evidence of association with concomitant therapy or other underlying conditions (grade of recommendation C).

### Cardiovascular manifestations

Two randomised controlled clinical trials (level of evidence 1b) conducted respectively with etanercept (153) and infliximab (154) in non-RA patients with advanced chronic heart failure (CHF, NYHA classes III and IV) failed to show a decrease in mortality and hospitalisations due to CHF with anti-TNF therapy. Moreover the ATTACH trial showed a trend towards a worse prognosis with high-dose infliximab in these patients (154). No increase in either CHF exacerbation or heart-failure related mortality was found among patients with RA and Crohn’s disease receiving TNF blocking agents (level of evidence 2b) (155-157).

Several studies showed a decreased risk of cardiovascular events (transient ischaemic attack, stroke, or myocardial infarction) in patients treated with TNF blockers (level of evidence 2b) (158-160). No data on cardiovascular disorders during abatacept, anakinra, and rituximab treatment have been published.

### Recommendations

- RA patients with no history of CHF and a concomitant indication for use of anti-TNF therapy do not need a baseline echocardiogram to screen for heart failure (grade of recommendation B).
- Patients with well-compensated, mild CHF (NYHA classes I and II) and a concomitant indication for use of anti-TNF therapy should have a baseline echocardiogram. Patients with a normal ejection fraction can receive therapy after a fully informed discussion with the patient and with close monitoring for any clinical signs or symptoms of worsening of heart failure. Anti-TNF therapy should be avoided in patients with a decreased ejection fraction (grade of recommendation B).
- In patients with NYHA classes III or IV heart failure, anti-TNF therapy is contraindicated (Grade of Recommendation B), as well as rituximab therapy in patients with NYHA class IV heart failure only (as indicated on product label).
- Patients who develop new-onset heart failure while on anti-TNF or rituximab therapy should have the therapy discontinued and should be evaluated for other causes of heart failure (grade of recommendation B).

### Liver function tests

Mild elevations in liver function tests have been reported in one observational study with TNF-blockers in up to 17% of patients, but increases exceeding more than twice the upper normal limit have been reported only in 2.1% out of 6861 patients (level of evidence 2b) (161). Concomitant drugs and associated clinical conditions may confound the interpretation of these data.
No data of hepatic toxicity have been reported in RCTs with Rituximab (33, 34), Abatacept (37-39) and Anakinra (41, 43) (level of evidence 1b).

Recommendation
• Patients on biological treatment should be monitored for hepatic safety according to patient-related risk factors (grade of recommendation D).

New onset of psoriasis and other skin disorders
The incidence of immune-mediated skin lesion is increased in patients treated with anti-TNF agents (level of evidence 3b and 4) (162-164). The most frequent manifestations are exacerbation of pre-existing psoriatic lesions and new-onset psoriasis (vulgaris, pustulosa, and psoriatic palmoplantar pustulosis mainly) (level of evidence 4 (165-174)), with a risk apparently higher in adalimumab treated patients (level of evidence 2b) (175); granuloma annulare, Stevens-Johnson’s syndrome, and skin vasculitis have also been reported (level of evidence 4) (163, 176, 177). In the majority of cases the local treatment of psoriatic lesions allowed to continue anti-TNF therapy without recrudescence of skin disease (level of evidence 4) (167, 168, 178, 179), although in more severe cases switching to another anti-TNF agent or withdrawal of the biologic treatment was necessary (level of evidence 4) (166, 180). Few cases of new-onset psoriasis during anakinra (181) and rituximab (182) therapy have also been reported (level of evidence 4). No data on skin toxicity during abatacept treatment have been published yet.

Recommendations
• When new-onset psoriasis occur during anti-TNF treatment, switch or withdrawal of biologic therapy is mandatory after failure of local management of skin lesions (grade of recommendation B).
• The persistence of skin lesions unresponsive to conventional local treatment is an indication to stop biologic therapy and to treat the skin disease with immunosuppressive agents. (grade of recommendation D).

Neurologic disorders
Case histories (level of evidence 4) report the possible association between anti-TNF-alpha treatment and demyelinating CNS lesions (183-187) and various disorders of peripheral nerve such as Guillain-Barré syndrome (188), Miller-Fisher syndrome (188), chronic inflammatory demyelinating polyneuropathy (189, 190), multifocal motor neuropathy with conduction block (191-193), mononeuropathy multiplex (194), and axonal sensorimotor polyneuropathies (195).

In the majority of cases, neurologic manifestations improve over a period of months after withdrawal of the TNF-α antagonist, with or without additional immuno-modulating treatment (level of evidence 4) (196). Some case-reports have been published on progressive multifocal leucoencephalopathy in SLE, RA and B-cell lymphoma patients treated with rituximab (level of evidence 4) (197, 198). No data on neurologic disorders during treatment with abatacept and anakinra have been published.

Recommendations
• Although anti-TNF related neurologic disorders are rare, anti-TNF therapy must be avoided in patients with a history of demyelinating disease (grade of recommendation D).
• Anti-TNF therapy must be immediately withdrawn when new neurologic signs and symptoms occur (grade of recommendation D).

Vasculitis
Although biological agents have successfully been used in isolated refractory cases of vasculitis, an increasing number of cases of vasculitis induced by biological agents (most of all anti-TNF, rarely rituximab or abatacept) have been described (level of evidence 4) (199-201). The clinical spectrum of vasculitic features was wide, but there was an overwhelming predominance of cutaneous involvement (in particular leukocytoclastic vasculitis) (202), renal involvement (203) and peripheral neuropathy (195). No data on vasculitides complicating anakinra and abatacept treatment have been published.

Recommendations
• In patients who develop this reaction, it is safer to stop the biologic therapy and treat with a regimen of steroids with or without immunosuppressive agents (grade of recommendation D).

Interstitial lung disease
The development of interstitial lung disease (ILD) in patients with rheumatic and autoimmune diseases treated with biologic therapies has been increasingly reported during last years (204-207); however there are no specific studies on the clinical presentation of this possible adverse event. In the vast majority of cases, ILD has been associated with anti TNF-alpha drugs, and two thirds of the ILD cases were treated with an association of methotrexate and biologic drugs. The incidence of ILD in biologic-treated RA patients varies from different studies and this may be due to a number of variables (ethnicity, underlying disease, type of study, drug availability in different countries, type of drug) (208, 209). However it seems that in RA patients treated with biologic agents the incidence of ILD is higher than in control patients (level of evidence 4). The main clinical features which may alert for a possible ILD are dyspnea, fever, cough. In these cases an exhaustive investigation is mandatory (lung function test, high-resolution pulmonary tomography, exclusion of an infectious disease) (level of evidence 2). Withdrawal of biologic therapy is recommended in these cases (level of evidence 4).

Recommendations
• When new-onset ILD occurs in patients treated with biologic agents, withdrawal of the drug should be recommended and an exhaustive investigation should be performed to exclude infectious disease (grade of recommendation D).
• In these patients, reinitiation of biologic treatment (especially with the same agent) is not recommended (grade of recommendation D).
• In patients with pre-existing ILD, anti-TNF agents should be avoided (grade of recommendation D).
Elective surgery
The occurrence of elective surgical interventions in rheumatic patients is a frequent condition (level of evidence 2b) (210). The real risk of complications in anti-TNF treated patients following surgical procedures remains unclear, but the peri-operative continuation of TNF blockers may cause surgical site infections and impaired wound healing (level of evidence 3b) (211-214). However, in the largest study focused on this item, peri-operative temporary discontinuation of biologic therapy has shown a trend toward a reduction in the risk of post-surgical complications (level of evidence 2b) (215). No data on the risk of surgical complications in patients receiving abatacept, rituximab, and anakinra have been published.

Recommendation
- In all patients with RA treated with biologic therapy undergoing elective surgery, the recommendation is to discontinue the treatment for a period of 2-4 times the half-life of the biologic agent according to the type of surgery (grade of recommendation C).

Pregnancy
Uncontrolled observations derived from case reports or registries found no increased foetal loss or miscarriages associated with the use of TNF blocking agents and suggest that conception and early pregnancy are not adversely affected by use of anti-TNF (pregnancy risk category B (216-225)). Uncommon adverse pregnancy outcomes observed with TNF inhibitor therapy appear to approximate those seen in women not receiving such therapy and may include premature birth, miscarriage, low birthweight, hypertension, and preeclampsia (level of evidence 4 (226-228)). A rare combination of congenital abnormalities (partial VATER defect – anal atresia and vertebral, tracheo-oesophageal, renal, cardiac and limb abnormalities) has been reported in association with etanercept therapy, but the causal relationship remains unclear (level of evidence 4 (229, 230)). Experience with rituximab in pregnant women is too limited to allow any statement on safety in pregnancy, but when administered in the 2nd and 3rd trimester, B cell depletion can occur in the foetus (level of evidence 4 (231-233)). No data on exposure to abatacept and anakinra during human pregnancy have been published (pregnancy risk category C).

Recommendations
- Although it is difficult to prove with certainty, data suggest that women who inadvertently become pregnant while taking anti-TNF agents can be reassured that continuation of pregnancy does not appear to hold any increased risk to either themselves or their baby (grade of recommendation C).
- In the absence of formal studies, the regular use of anti-TNF therapies during pregnancy cannot be advocated and anti-TNF agents should be withdrawn when the patient becomes pregnant (grade of recommendation C).
- Because of the lack of definitive data and according to product label indications abatacept and rituximab should be discontinued 14 and 52 weeks respectively before a planned pregnancy (grade of recommendation D).

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