TITLE: **The use of anti-TNF-alpha therapies for patients with Systemic Lupus Erythematosus. Where are we now?**

Ana Lorenzo-Vizcaya[1], David A. Isenberg[2]

[1] Department of Internal Medicine, Hospital Universitario De Ourense. Ourense, Spain

[2] Department of Rheumatology, Division of Medicine, University College London. London, UK

Address for Correspondence:

Professor David Isenberg

Room 423 The Rayne Building

University College London

5 University Street

London WC1E 6JF

E mail Address: d.isenberg@ucl.ac.uk

ARTICLE HIGHLIGHTS:

- TNF-alpha of the main proinflammatory cytokines playing a key role in autoimmune diseases such as RA or SLE, so anti-TNF-alpha therapies could be a therapeutic option in SLE patients
- Nowadays, biologic drugs as anti-TNF-alpha are widely used for the treatment of diseases such as RA or psoriatic arthritis, but they are not a first-line option to treat SLE patients.
- Anti-TNF-alpha drugs were explored rather transiently for the treatment of SLE when they were first developed.
- We have reviewed the published data to ask the question were they prematurely 'abandoned'
- We summarize the clinical beneffits and the main adverse effects reported in many different studies of patients under anti-TNF-alpha therapies.
- Adverse effects on TNF-alpha inhibitor remain unclear, so patients receiving these therapies must be closely followed-up and physicians should be aware of signs or symptoms that could suggest that we are facing a lupus-like syndrome.

**ABSTRACT:**

Introduction: Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease characterized by multiple pathologies in which sustained inflammatory activity leads to progressive tissue destruction and organ damage. One of the main proinflammatory cytokines playing a key role in autoimmune diseases such as rheumatoid arthritis (RA) or SLE, is tumor necrosis factor (TNF) alpha.

Areas covered: The introduction of TNF-alpha inhibitors revolutionized the treatment of RA and other conditions including psoriatic arthritis and ankylosing spodylitis. We review here the efficacy and safety of TNF-alpha blockers in SLE focussing on why it has not been more widely used since TNF-alpha was reported to be increased in SLE patients and to correlate with disease activity .

Expert opinion: We summarize the reported SLE cases that have received TNF-alpha blockers and the main results to date. We reflect on whether there is a case to reconsider the use TNF-alpha blockade in SLE.

Key words: SLE, infliximab, TNF-alpha, targets, biologics, lupus nephritis.

**INTRODUCTION**:

Systemic lupus erythematosus (SLE) is a potentially sinister autoimmune rheumatic disease characterized by breakdown of self tolerance, B cell hyperactivity, autoantibody production, aberrant formation of immune complexes, and inflammation of multiple organs [1] The consequent tissue destruction and organ damage, leads to a variety of clinical manifestations of SLE; notably arthritis, skin rashes and lupus nephritis.

The current prognosis is much better than 50 years ago due to earlier diagnosis, the more rational use of corticosteroids and immunosupressive (IS) drugs, the availability of dialysis and transplantation and an increased awareness of concomitant diseases [2]. Most symptoms and disease activity are controlled with corticosteroids, hydroxychloroquine (HCQ) and IS drugs, notably azathioprine (AZA), cyclophosphamide, cyclosporine or mycophenolate mofetil (MMF) [3]. However, the course of SLE is unpredictable and flares are frequent, inspite of seemingly adequate treatment.

- <u>The role of tumor necrosis factor (TNF) alpha:</u>

TNF-alpha is a proinflammatory cytokine with pleiotropic properties and functions including the activation of a cascade of inflammatory events leading to tissue destruction [4]. This cytokine is part of the inflammation cascade, and its activation results in inflammatory signaling by NF-κB, which in turn activates the transcription of proinflammatory gene targets such as interleukin1β (IL-1β), IL-6, and IL-8 [5].

Thus TNF-alpha constitutes one of the main mediators of inflammation and tissue damage in autoimmune diseases. As we will discuss below, it is important to mention that TNF-alpha has a dual role in human and animal renal autoimmune diseases: on the one hand, it is associated with inflammatory activation but on the other, it has been shown that TNF-alpha protect NZB lupus prone mice from developing nephritis [6].

- <u>TNF alpha in murine lupus prone models:</u>

Several mouse strains, develop autoimmune disorders very similar to human SLE [7]. TNF-alpha is known to play a role in lupus prone animal models, being a cytokine with an immunoregulatory function; although this action is not uniform and its role differs depending on the stage of disease. Lupus prone mice develop immune-complex mediated tissue injury, notably involving the kidneys, joints or the pulmonary system.

In 1988 Jacob et al. [8] noted that NZB/W mice (a lupus prone strain) had a lower production of TNF compared to NZW (the healthy mouse strain). They showed that the disease in the NZB/W mice, was partly reversible by the early administracion of recombinant TNF. They demonstrated that a genetic deficiency in TNF plays a significant role in the onset of autoimmunity in these mice. A year later, Gordon et al. [9], repeated the studies with murine models and extended them. They observed beneficial effects with the administration of high dose TNF, even if they had developed nephritis before treatment. In their study they observed however, that protection against the disease was not long-term. These findings were supported by Kontoyiannis et al. [10] who reported that TNF-deficient mice, NZB/W, developed a severe lupus-like disease.

In the same way, it was demonstrated by histological analysis, that TNF-alpha blockade in NZB/W mice leads to a reduction of infiltration of mononuclear cells in the joints, lungs and skin [11]. Treated NZB/W mice showed an improvement in symptoms, notably no swelling of the joints was

observed and there was an absence of alopecia. It was also noted that treated mice had an increased lifespan compared to those who were not treated. Thus, TNF blockers were shown to be beneficial for arthritis, pneumonitis, and skin disease in this murine strain.

With respect to renal disease, it was observed that late administration (at four months of age) of low-dose of TNF-alpha blocker to NZB/W mice resulted in accelerated renal damage [12]. In contrast, when treatment was administered from 2-4 months of age, renal disease was not accelerated [12]. Thus TNF-alpha is required to suppress autoimmunity, but paradoxically, its presence in older mice may exacerbate the development of renal pathology; revealing that TNF-alpha has different roles at different stages of lupus immunopathology.

Around this time it was reported that MRL/lpr lupus-prone mice had increased levels of TNF mRNA in their lungs, compared to control mice [13]. These data suggest that TNF alpha plays an important role in the development of pulmonary inflammation in this mouse model. In view of this, subsequently an immunoglobulin (Ig) G anti-TNF antibody was injected into lupus-prone and control mice. After that, the pulmonary tissues of both mice groups were examined and pulmonary inflammation was found to be significantly reduced in the treated lupus-prone mice, compared to the controls [13].

Following these beneficial reports of anti-TNF therapy in lupus prone mice; it was suggested that TNF blockade might also be useful in humans with SLE [14].

- <u>TNF-alpha in humans:</u>

TNF-alpha is overexpressed in humans with rheumatic diseases like rheumatoid arthritis (RA), spondylarthropathies (SpA) or SLE. With regard to SLE, high levels of TNF-alpha were observed in serum of lupus patients [15, A] and these elevated serum and gene expression levels are positively associated with disease activity, notably in those with renal involvement [15].

Gómez et al [16], measured circulating levels of Th1 and Th2 cytokines in patients with SLE with the objective of determining their association with disease activity. They observed that SLE patients with both active and inactive disease, had significantly higher levels of TNF-alpha than controls ($p<0.01$). Interestingly, it was also noted that patients with inactive disease had statistically higher levels than those with active disease ($p<0.01$) [16].

Thus the idea that blocking TNF-alpha in lupus patients, especially those with renal involvement seemed appropriate; but its use remains controversial because it is thought that TNF-alpha is a cytokine with a dual role in SLE. It may act as a proinflammatory factor released in local tissues during periods of active disease but also an immunosupressive mediator chronically produced, and involved in the development, differentiation and regulation of immune cells, as part of a defense mechanism [16,17].

- <u>TNF-alpha blockers in humans with rheumatic diseases.</u>

Biologic disease-modifying anti-rheumatic drugs (bDMARDs), can be categorized according to their mechanism of action, and the first to be recognised were those that inhibit TNF-alpha [18]. They are now widely used in this field for the treatment of diseases such as rheumatoid arthritis (RA), psoriatic arthritis or ankylosing spondylitis (AS). Conventional DMARDs, most commonly methotrexate (MTX), but also including sulphasalazine, HCQ, leflunomide and ciclosporin, are usually the first choice drugs. When they do not achieve remission, biologics (alone or added to conventional DMARDs) are now widely used to control active disease, following the guidelines of the

American College of Rheumatology (ACR) [19] and the European League Against Rheumatism (EULAR) [20] for the management of RA.

Analogous to the introduction of biologics for the treatment of RA, psoriatic arthritis and ankylosing spondylitis many attempts have been made to identify successful biologic agents for lupus [21,22].

Since anti-TNF-alpha monoclonals, are able to block the immune mechanisms, it was tempting to speculate that they might be effective in the treatment of SLE, where immune complexes are likely to be playing a role. There was some initial encouragement that this approach was successful (discussed in more detail below) but later studies were not as encouraging. Currently, TNF-alpha blocking molecules are not recommended as the initial treatment of SLE and they are limited to refractory cases [23].

Given the recent failure of so many biologic drugs in the treatment of SLE [24] we thought it might be worthwhile re-examining the potential of biologic approaches that might jhave been abandoned prematurely. Thus, in this review we re-consider the potential for TNF-alpha blockade and ask what part, if any, these drugs might yet play in treating SLE patients.

**CLINICAL BENEFITS OF ANTI-TNF-ALPHA IN LUPUS PATIENTS:**

Disappointingly, reviewing the literature, the evidence that supports the use of anti-TNF therapies in SLE remains limited. There are relatively few published studies that involve substantial numbers of patients so far. These cases are summarised in Table 1. It demonstrates that infliximab and etanercept have been the TNF-alpha blockers most commonly used. The patients shown in Table 1, all fulfilled the revised ACR [19] criteria for SLE [25]; with persistent activity disease despite conventional treatment.

Arthritis:

In 2004 an open-label trial [26] of infliximab added to azathioprine or methotrexate, that included three patients with refractory lupus polyarthritis was published. A few days after the first infusion, each patient went into complete remission, with reduction in joint swelling and tenderness. The effect lasted for about eight weeks after the last of four infusions in two of the three patients. The other patient, had a relapse 11 weeks after the last dose of infliximab.

In another study [27] a patient with severe polyarthritis, despite the use of corticosteroids, MTX, AZA and HCQ, was given infliximab. The patient went in to sustained remission which continued despite the subsequent tapering of her steroids and stopping AZA and MTX.

Cortés-Hernández et al. [28] studied the effects of etanercept on 35 patients with refractory lupus arthritis. They added this TNF-alpha blocker to the conventional IS therapy and observed that 92% of patients with joint involvement achieved remission. The response was assessed by complete resolution of the symptoms or by a score < 4 using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [29].

Another more recent open-label study [30] looked at the long term effects of etanercept and adalimumab in SLE. Fifteen patients were assessed: 12 treated with etanercept, for a median duration of 62.5 months; and three received adalimumab for a median of 36 months. Before being included in the study, 11 patients were treated with methotrexate and eight with HCQ; and thus they had active disease in spite of being treated with usually adequate conventional therapy. During the observation period, the median prednisone dose decreased significantly from 15mg/day to 5

mg/day ($p<0.01$). These data support the idea that anti-TNF agents can be useful in the treatment of refractory lupus arthritis.

Cardiopulmonary manifestations:

In the study of etanercept referred to above [28], ten patients had refractory serositis and six shrinking lung syndrome (SLS). Eight out of ten with pleuropericarditis achieved clinical remission in a mean time of 5.67 weeks. In four patients (80%) with lung involvement, the Forced Vital Capacity (FVC) rose from 43% to 58% at the end of the treatment. This increase was statistically significant ($p<0.05$). However, relapse was frequent, occurring 8-11 weeks after stopping etanercept.

Skin:

TNF-alpha expression was also demonstrated by skin biopsy of four patients with refractory subacute cutaneous lupus erythematosus (SCLE) [31]. In this study, both lesional and non-lesional skin of patients with SLCE was biopsied, and in the immunohistochemical study of refractory lesional skin tissue moderate to strong staining of TNF-alpha was identified in the lesional epidermis of all four cases.

Data about the clinical effectiveness of TNF-alpha blockade on lupus rashes are limited. There have been two published cases of patients with SCLE who were treated with TNF-alpha blockers. One of the patients received treatment with the combination of infliximab and azathioprine [32], and the other was given etanercept [33], and in both patients an improvement of the butterfly rash was noted.

The efficacy of etanercept given by low-dose (10 mg) intradermal weekly injection, was also investigated in 25 patients with discoid lupus erythematosus, refractory to anti-malarials [34]. Clinical improvement was noted, on skin manifestations notably erythema, induration and scaling; defined by a reduction of 20% in total activity of the modified limited Score of Activity and Damage in Discoid Lupus Erythematosus (ML-SADDLE) 20 response at week 12. Intradermal etanercept was well tolerated and there were no observed systemic TNF effects or any major safety issues. Multi-centre trials are however needed to determine the overall and long term benefit of this therapy.

Nephritis:

There are very few reports of patients with lupus nephritis (LN) being treated with TNF-alpha blockers. We have identified only 12 such patients.

Aringer et al. published a case series in 2004 [26], that included four LN patients one had World Health Organisation (WHO) class III nephritis, two had diffuse proliferative, WHO class IV; and the other, had membranous LN, WHO class V [26]. Their proteinuria had not been well controlled in spite of conventional IS therapies. They received four 300-mg doses of infliximab in addition to AZA or MTX. The addition of the TNF-alpha blocker to conventional treatment, led to significant renal responses with improvement in their proteinuria over time, reaching the lowest level at about week eight; and by a stable or slightly improving renal function in all patients. The mean creatinine clearance rate was 79 $\pm$29 SD ml/minute at baseline and 100 $\pm$32 SD ml/minute at week 20. After the last infliximab infusion, proteinuria levels remained low for more than six months [26].

Some single cases of SLE patients who received anti-TNF therapies have been published. One of these reported by Hayat et al. [35], described the safety and efficacy of infliximab given to a patient with an SLE (with WHO class IV nephritis) relapse despite conventional IS therapy. One month after infliximab, the urinary sediment ameliorated and proteinuria decreased from 3.7 g/24h to 0.391

g/24h, so that her steroids could be reduced. This remission was maintained six months after the last infusion. Another single case [2], of a patient with renal involvement treated with a TNF-alpha blocker, was young a woman with persistently active disease despite conventional treatment, with a SLEDAI score of 24. She also developed Cushing's syndrome due to corticosteroids. Etanercept (50 mg/weekly) was given with a good response; the patient's complement levels normalised and her SLEDAI reduced to 4. Later, she got pregnant and had a relapse of her lupus with proteinuria. The persistence of proteinuria implied on going active LN, so plasmapheresis and intravenous gammaglobulin (IVGG) therapy were added with a beneficial response [2]. After giving birth, a kidney biopsy confirmed the LN (WHO class IV). They concluded that etanercept may be safe and perhaps effective for SLE pregnant women with severe LN [2].

In 2009 Aringer et al. [36] reported the long-term follow-up, (> 4 years) data of 13 infliximab treated patients with SLE. They proposed that an induction regimen of four infusions of the TNF-alpha blocker infliximab, combined with background immunosuppression, can achieve significant improvement in patients with refractory LN and such benefit seemed to last for at least four years [36]. In this study, they compare the results of a long-term regimen of infliximab with short-term therapy (four infusions of about 5 mg/kg of infliximab at week 0, 2, 6 and 10). Three patients received a longer-tem regimen of infliximab: one received 16 infusions (up to 15 months after induction), eight (10 months of treatment after induction) and the final patient had six (two additional infusions to induction). During the follow-up period, they noted that short-term infliximab therapy had maintained low levels of proteinuria and inactive urinary sediment but the prolonged regimens showed no additional benefit in comparison [36]. Notably they also observed an increase in mortality due to infections and an increased incidence of lymphomas in patients who received prolonged treatment with an anti-TNF while they patients under short-term therapy did not have any increased risk of life-threatening adverse event [36]. SLE patients have a higher mortality rate related to infections and an increased incidence of lymphomas [37,38] (although the absolute numbers of cases are small); so the authors considered that these fatal effects may be an unfortunate coincidence in severely sick patients rather than association with TNF-alpha blockade per se [36].

Aspects of Assessing Disease Activity:

In the studies detailed in the previous sections lupus activity was measured by the SLEDAI and by monitoring changes in laboratory parameters (e.g: levels of complement, anti-double stranded DNA (ds-DNA) autoantibodies, proteinuria).

In the open label study with infliximab reported in 2004 [26] none of the six patients had an increase in disease activity while receiving infliximab during a subsequent period of up to 52 weeks of observation. Later in 2006, Micheloud et al. reported a single case detailed above [2], showing that after treatment with etanercept, SLEDAI reduced from 24 to 4 points; and in 2009, Uppal et al. [39] evaluated the impact of TNF-alpha blockade with infliximab on disease activity. This study included 46 patients (27 with lupus and 19 healthy control). Of the lupus patients, 18 were allocated to control arm, receiving conventional treatment consistent with EULAR guidelines [40]. The other nine were allocated to treatment arm, and they received infliximab in addition to conventional treatment. In this study it was observed that this treatment group showed a significant improvement in SLEDAI with a reduction in the mean score from 28 to 13 ($p<0.035$). A reduction in the corticosteroid requirement from a mean dose of 47.5 mg/d at baseline to 8.75 mg/d after six months of treatment with infliximab, was also observed in the treatment group; whereas control group needed to increase corticosteroid dose from 37.5 mg/d to 41. 50 mg/d ($p<0.052$) [39].

Finally, in another open label study of 15 patients treated with etanercept [28] the SLEDAI decreased significantly from 6 to 4 ($p<0.001$)

**SIDE EFFECTS OF ANTI-TNF-ALPHA**:

Clinical side effects:

TNF has a main role in host defense and protection against intracellular bacteria, so its blockade might theoretically predispose to infectious complications. And an increase in the risk for infections in patients with RA receiving anti-TNF-alpha therapies [41,42] has been noted. Nevertheless, this risk for infections varies over time, as was reported in a study undertaken by the British Society for Rheumatology Biologics Registry (BSRBR) [43] in which a significantly increased risk for infection was observed within the first 90 days after starting treatment.

It was also thought that patients receiving anti-TNF therapies might have an increased risk of lymphomas [42], but many studies and registry databases published in the past decade, found no association between anti-TNF treatment and the new onset of solid or hematologic cancers [44,45].

Infections were the main undesired side effects reported in the studies of patients with SLE mentioned above. Aringer et al. [26] reviewed three cases of urinary tract infection, and one complicated by bacteremia in their study. Notably these patients had had similar urinary tract infections during the year before infliximab therapy. In one study with etanercept [28] whose aim was to evaluate its efficacy and safety in patients with moderately active SLE, the main side effects observed were local reactions (14%) followed by urinary tract infection (5%).

Among life-threatening complications, *Legionella* pneumonia and cerebral lymphoma have been described in SLE patients on long term therapy [36]. It is difficult to know however, if these problems were related solely to anti-TNF therapy or linked to the many other IS drugs with which the patients had been treated previously. It is also known that SLE patients have increased risk of infections [42] and an associated increased mortality [46], and they have a small absolute increased incidence of lymphomas [47].

In 2010, six patients with RA or psoriatic arthritis who developed SLE with life-threatening manifestations after receiving an anti-TNF to their arthritis, were reported [48]. The most severe manifestations observed were: pericarditis and neuropsychiatric SLE (notably optic neuritis, headaches and major depression), renal disorders and cutaneous SLE.

Laboratory "side effects":

The use of TNF-alpha blockers in autoimmune diseases has been linked to the emergence of anti-nuclear antibodies (ANAs) and anti-dsDNA [49]. Most of the later were IgM isotype, the G isotype being much less frequently observed [49]; this isotype being more closely associated with the development of clinically overt SLE [50]. Thus, some patients may also develop clinical symptoms similar to idiopathic lupus and when it occurs, it is considered to be a anti-TNF-induced lupus (ATIL) [51]. Picardo et al. [52] carried out a study to evaluate the incidence and clinical and serological markers of ATIL in patients on anti-TNF-alpha therapies. They reported a higher incidence of ATIL in patients on infliximab (5.7%) comparing to adalimumab (0.6%) [52].

With regard to new onset of autoantibodies in patients receiving infliximab therapy, ANAs were observed from 17% to 71% and ds-DNA from 9% to 54% [53-65].

However, the presence of these antibodies was often transient and their levels fell back to baseline levels shortly after TNF-alpha blocker was stopped [26,50].

In one of the trials with infliximab [26], it was noted that in four of six patients, anti-dsDNA levels increased, around the time of fourth infusion, although this rise was not linked to a significant increase in disease activity. Four of six patients also had a transient increase in IgM anti-cardiolipin antibodies; and one also developed an IgG anti-cardiolipn antibody. Despite this, no vascular events were observed during the 52 weeks follow-up period.

In another open-label trial that included 7 patients [50] five out of seven SLE patients given TNF-alpha blocker (short-term infliximab), increased the titre of their anti-dsDNA antibodies. Four out of seven patients had a rise in IgM anti cardiolipin antibodies. All antibody types peaked 4-10 week after the last infliximab infusion and, after reaching a peak, these levels decreased to pretreatment levels or lower. It is worth mentioning that the anti-histone and anti-chromatin reactivity noted during TNF blockade in patients with lupus also rapidly decreased to levels below baseline [50].

Soforo et al. [48] reported six cases who developed active SLE after receiving TNF-alpha blockers for treatment of RA or psoriatic arthritis. Before commencing anti-TNF therapy, three out of six had positive ANA (1/1250), one was negative and the ANA status of the other two, was unknown. After starting anti-TNF-alpha treatment, all six patients were noted to be ANA positive, and the titres of those previously positive, were higher: four at dilutions of 1/2560 and two, 1/1280 [46]. This observation suggest that TNF blockers may be a trigger ANA production with the consequent lupus-like syndrome. Thus, patients treated with these therapies, should be closely monitored.

In another study [28] that included 42 lupus patients, the authors observed that levels of ANA and/or anti-dsDNA antibodies, rose in six. A more recent study [66] total of 112 patients with RA and AS were enrolled. Fifty six were patients who had that received anti-TNF-alpha drugs and the other 56 were controls that had only received non-biological drug treatment. They followed-up these patients for four months after treatment with infliximab and etanercept, and observed that ANA were positive in five (36%) patients with RA treated with infliximab and none of the control group were ANA positive ($p<0.0003$). Anti-dsDNA were positive in three (21%) of these patients while none of control group had these antibodies ($p<0.025$). In those patients with RA who received etanercept the ANA tests were positive in four (28%) compared to no positives in the control group ($p<0.009$). There were non significant ($p=0.15$) differences with respect to ds-DNA antibodies. In patients with SA, ANA were positive in three (28%) of those treated with infliximab and none in control group ($p<0.025$). Only one patient with AS treated with infliximab developed anti-dsDNA antibodies (7%) and there were no positive anti-dsDNA antibodies in the control group, but this was not statistically significative different ($p=0.15$). Finally, of those AS patients who were on etanercept, two (14%) had positive ANA tests and one (7%) had detectable anti-dsDNA antibodies compared to no patients with ANA or anti-dsDNA antibodies in the control group, but these findings too were not statistically significant ($p=0.63$ and $p=0.15$, respectively) [66]. None of these patients met the full critera for SLE, based on Systemic Lupus International Collaborating Clinic (SLICC) criteria set [67].

Despite these findings, the induction of clinically overt lupus-like disease by TNF-alpha blockers seems to be uncommon [47,68]; and in some studies none of the patients experienced a lupus flare. Their serum complement levels remained stable during TNF-alpha blockade [26,28,50].

In 2018 a study [69] was published describing the use of VigiBase (the WHO global individual case safety reports database (ICSRs)). In this database, among 12.166 of drug-induced lupus patients the drugs most likely to be linked to the development of SLE were identifyied [69].

When this form of drug induced SLE develops, it is manifested by a variety of symptoms including fatigue, fever, musculoskeletal, serositis or skin symptoms [70]. Renal and central nervous system

(CNS) involvement are however, rare [51,71] Nevertheless, seven cases of nephritis have been reported in patients prescribed anti-TNF therapy. Of these, four patients were on etanercept, two infliximab and one was receiving adalimumab [55].

With respect to CNS involvement, an increasing number of neurological side effects notably demyelinating events, in patients on TNF-alpha blockers have been reported [72]. In 2017 a review of the 122 published cases of CNS demyelination associated with anti-TNF-alpha therapy was published [73]. Although over 2 million patients with rheumatic and inflammatory diseases have been treated with TNF-alpha blockers, the overall number of patients that developed demyelinating events is relatively small. In this review, the authors concluded that there could be a causal association between this biologics and CNS demyelination [73]. One arguments that supports this relationship is the delayed onset of demyelination among the RA patients registered (mean age 45.47 years) in contrast to the peak age of multiple sclerosis (MS) onset (20-40 years old) [73].

Changes in blood counts, notably neutropenia, have also been reported in patients under treatment with TNF-alpha blockers [74-77]. In addition cases of anemia [78] and thrombocytopenia [79-81] although uncommon, have been reported but they were not associated with serious adverse events [82].

Recently, a case-control study [83] was published in which the association between drug use and subsequent diagnosis of SLE registered in the Danish Patient Register (from January 1, 2000 to December 31, 2017) was examined. The study population included 3148 patients with cutaneous lupus erythematosus (CLE) or SLE. In the post hoc analyses for TNF-alpha inhibitors, an increased Odds Ratio (OR) was found for CLE (OR 4.96 [95% CI, 2.30-10.71]) and also for SLE (OR 3.64 [95% CI, 1.93-6.89]) [83].

On balance though, it seems clear that the lupus-like syndromes induced by TNF-alpha blockers, are usually benign and resolve after the anti-TNF monoclonal is stopped [70,71], although fully recovery can take several moths [84,85].

**CONCLUSION**:

Anti-TNF alpha therapies have been widely used in autoimmune disorders, specially in RA. However, in lupus patients, their use has invariably been restricted to specific cases, mainly those refractory to conventional IS drugs.

Initially, trials with TNF-alpha blockers were also carried out in lupus patients, but perhaps because of the observation of the development of autoantibodies, notably ANAs and ds-DNA; the use of these drugs as a first-line treatment was regarded as too much of a risk. It was perhaps counter intuitive to use this approach in SLE.

Because the adverse effects on TNF-alpha inhibitor remain unclear, patients receiving these therapies must be closely followed-up and physicians should be aware of signs or symptoms that could suggest that we are facing an ATILS.

Based on the results observed in the trials published to date, it has been reported that TNF-alpha blockers are a relatively safe and effective therapeutic target for the treatment of lupus patients, notably in those with arthritis as dominant feature and perhaps in LN where a significant reduction in proteinuria has been noted. The development of autoantibodies usually found in SLE, after TNF alpha blockade is started; while relatively common, does not seem to lead to an increase in lupus activity. Another point to take into account is the fact that in clinical trials, SLE patients with a severe relapse of the disease are usually excluded. Therefore, the results observed in the published

single cases of lupus patients with severe disease flares, in which clinical improvement was documented; would support the use of these therapies even in the most seriously ill patients.

Thus, taking these data together, the fact that benlysta and rituximab apart, no monoclonals have been widely used in SLE and the good long term safety profiles of the TNF-alpha blockers it could be time, cautiously, to reconsider undertaking randomized controlled trials of these monoclonals in both established SLE and early in the course of the disease. It is worth emphasizing the importance of closely monitoring symptoms and laboratory parameters that might anticipate a relapse or an increased disease activity.

**EXPERT OPINION:**

The cytokine TNF-alpha may well be involved in aspects of lupus pathogenesis. Monoclonal anti-TNF α antibodies are widely used in patients with other rheumatic diseases, including RA, psoriatic arthritis and ankylosing spondylitis. The use of these antibodies in SLE has been reported. However this approach is not routine in SLE for reasons, which are a little opaque. Knowing their potential side effects is also of value.

Given the early successes of TNF α blockade in SLE, the paucity of published clinical trials is odd. Successes were recorded with some renal lupus patients as well as those with 'hard-to-treat' joint disease and other manifestations.

The objective of this review is to ask the question whether the apparent abandonment of the use of TNF α blockers in SLE was premature.

One concern about the use of this approach has been reports of the development of anti-dsDNA antibodies after starting treatment. However in the main these appear to be of the IgM isotype and there are very few cases of patients with RA, given TNF α blockers who 'transform' into clinically overt lupus. Thus it may be that caution about using TNF α blockers has been 'overblown'.

In the next few years, it would be interesting to carry out trials with TNF α blockers, to help achieve the control of lupus earlier in the course of the disease. .

**REFERENCES:**

1.- Manson JJ, Isenberg DA. The pathogenesis of systemic lupus erythematosus. *The Netherlands Journal of Medicine.* 2003;61(11):343-346.

2.- Micheloud D, Nuño L, Rodríguez-Mahou M, et al. Efficacy and safety of Etanercept, high-dose intravenous gammaglobulin and plasmapheresis combined therapy for lupus diffuse proliferative nephritis complicating pregnancy. *Lupus.* 2006;15(12):881–885.

3.- Carreño L, López-Longo FJ, González CM, et al. Treatment options for juvenile-onset systemic lupus erythematosus. *Paediatr Drugs*. 2002;4(4):241-256.

4.- O'Shea JJ, Ma A, Lipsky P. Cytokines and autoimmunity. *Nat Rev Immunol.* 2002;2(1):37-45.

5.- Wu AJ, Hua H, Munson SH, et al. Tumor necrosis factor-alpha regulation of CD4+CD25+ T cell levels in NOD mice. *Proc Natl Acad Sci U S A*. 2002;99(19):12287-12292.

6.- Boswell JM, Yui MA, Burt DW, et al. Increased tumor necrosis factor and IL-1 beta gene expression in the kidneys of mice with lupus nephritis. *Journal of Immunology*. 1988;141(9):3050-3054.

7.- Andrews BS, Eisenberg RA, Theofilopoulos AN, et al. Spontaneous murine lupus-like syndromes. Clinical and immunopathological manifestations in several strains. *J Exp Med*. 1978;148(5):1198-1215.

8.- Jacob C, McDevitt H. Tumour necrosis factor-α in murine autoimmune 'lupus' nephritis. *Nature.* 1988;331:356-358.

9.- Gordon C, Ranges GE, Greenspan JS, et al. Chronic therapy with recombinant tumor necrosis factor-alpha in autoimmune NZB/NZW F1 mice. *Clin Immunol Immunopathol*. 1989;52:421-434.

10.- Kontoyiannis D, Kollias G. Accelerated autoimmunity and lupus nephritis in NZB mice with an engineered heterozygous deficiency in tumor necrosis factor. *Eur J Immunol.* 2000;30:2038-47
11.- Su X, Zhou T, Yang P et al. Reduction of arthritis and pneumonitis in motheaten mice by soluble tumor necrosis factor receptor. *Arthritis Rheum*. 1998;41(1):139-149.

****Description of clinical beneffits of TNF-alpha blockers in some manifestations in lupus prone mice.**

12.- Brennan DC, Yui MA, Wuthrich RP, et al. Tumor necrosis factor and IL-1 in New Zealand Black/White mice. Enhanced gene expression and acceleration of renal injury. *J Immunol*. 1989;143:3470-3475

13.- Deguchi Y, Kishimoto S. Tumour necrosis factor/cachectin plays a key role in autoimmune pulmonary inflammation in lupus-prone mice. *Clin Exp Immunol*. 1991;85:392-395
14.- Aringer M, Smolen JS. Therapeutic blockade of TNF in patients with SLE-promising or crazy? *Autoimmunity Reviews*. 2012;11(5):321-325.

15.- Takemura T, Yoshioka K, Murakami K, et al. Cellular localization of inflammatory cytokines in human glomerulonephritis. *Virchows Arch*. 1994;424(5):459-464.

16.- Gómez D, Correa PA, Gómez LM et al. Th1/Th2 cytokines in patients with systemic lupus erythematosus: is tumor necrosis factor alpha protective? *Semin Arthritis Rheum*. 2004;33(6):404-413.

17.- Mageed RA, Isenberg DA. Tumour necrosis factor alpha in systemic lupus erythematosus and anti-DNA autoantibody production. *Lupus*. 2002;11(12):850-855.

18.- Scott DL, Kingsley GH. Tumor necrosis factor inhibitors for rheumatoid arthritis. *N Engl J Med.* 2006;355(7):704-712. D

19.- Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol*. 2016;68(1):1-26.

20.- Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis*. 2014;73(3):492-509.

21.- Ciurtin C, Isenberg DA. Biologicsin Rheumatology: New developments, clinical uses and health implication. New York (NY): *Nova Biomedica*l; 2016

22.- Lorenzo-Vizcaya A, Fasano S, Isenberg DA. Bruton's Tyrosine Kinase Inhibitors: A New Therapeutic Target for the Treatment of SLE?. *Immunotargets Ther*. 2020;9:105-110.

23.- Samotij D, Reich A. Biologics in the Treatment of Lupus Erythematosus: A Critical Literature Review. *Biomed Res Int*. 2019;2019:8142368.

24.- Murphy G, Isenberg DA. New therapies for systemic lupus erythematosus - past imperfect, future tense. *Nat Rev Rheumatol*. 2019;15(7):403-412.

25.- Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1997;40:1725.

26.- Aringer M, Graninger WB, Steiner G, et al. Safety and efficacy of TNFa blockade in systemic lupus erythematosus – an open label study. *Arthritis Rheum*. 2004;50:3161-3169.

***Assessment of infliximab in SLE patients.**

27.- Hayat SJ, Uppal SS. Therapeutic efficacy and safety profile of infliximab in active systemic lupus erythematosus. *Mod Rheumatol*. 2007;17(2):174-177.

28.- Cortes-Hernandez J, Egri N, Vilardell-Tarres M, et al. Safety and Efficacy of Etanercept in Systemic LUPUS Erythematosus. *2012 ACR/ARHP Annual Meeting*: Abstract Number 1432.

***Assessment of Etanercept in SLE patients.**

29.- Bombardier C, Gladman DD, Urowitz MB, et al. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum*. 1992;35(6):630-640.

30.- Danion F, Sparsa L, Arnaud L, et al. Long-term efficacy and safety of antitumour necrosis factor alpha treatment in rhupus: an open-label study of 15 patients. *RMD Open*. 2017;3(2):e000555.

***Assessment of long-term effects of TNF-alpha inhibitors (etanercept and adalimumab) in lupus patients.**

31.- Zampieri S, Alaibac M, Iaccarino L, et al. Tumour necrosis factor alpha is expressed in refractory skin lesions from patients with subacute cutaneous lupus erythematosus. *Ann Rheum Dis*. 2006;65(4):545-548

32.- Hiepe F, Bruns A, Feist E, et al. Successful treatment of a patient suffering from a refractory subacute cutaneous lupus erythematosus (SCLE) with blockers of tumour necrosis factor a [abstract] *Arthritis Rheum*. 2004;50:S413

33.- Norman R, Greenberg RG, Jackson JM. Case reports of etanercept in inflammatory dermatoses. *J Am Acad Dermato*l. 2006;54:S139-S142.

34.- Md Yusof M, Wittmann M, Fernandez C, et al. FRI0328 Targeted therapy using intradermal injection of etanercept for remission induction in discoid lupus erythematosus (TARGET-DLE): first results from a proof-of-concept phase 2 trial. *Annals of the Rheumatic Diseases.* 2018;77:700-701.

35.- Hayat SJ, Uppal SS, Narayanan Nampoory MR, et al. Safety and efficacy of infliximab in a patient with active WHO class IV lupus nephritis. *Clin Rheumatol*. 2007;26(6):973-975.

36.- Aringer M, Houssiau F, Gordon C, et al. Adverse events and efficacy of TNF-alpha blockade with infliximab in patients with systemic lupus erythematosus: long-term follow-up of 13 patients. *Rheumatology*. 2009;48(11):1451-1454.

37.- Bernatsky S, Ramsey-Goldman R, Isenberg D, et al. Hodgkin's lymphoma in systemic lupus erythematosus. *Rheumatology*. 2007;46(5):830-832.

38.- Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med*. 2005;165(20):2337-2344.

39.- Uppal S, Hayat S, Raghupathy, R. Efficacy and safety of infliximab in active SLE: a pilot study. *Lupus.* 2009;18(8):690-697.

*** Provides information about safety and efficacy of infliximab in active SLE**

40.- Bertsias G, Ioannidis JP, Boletis J, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis*. 2008;67(2):195-205.

41.- Bongartz T, Sutton AJ, Buchan I, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA*. 2006;295:2275-2285.

42.- Listing J, Strangfeld A, Kary S, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. *Arthritis Rheum*. 2005;52(11):3403-3412.

43.- Dixon WG, Symmons DP, Lunt M, et al. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. *Arthritis Rheum*. 2007;56:2896-2904

44.- Pereira R, Lago P, Faria R, et al. Safety of Anti-TNF Therapies in Immune-Mediated Inflammatory Diseases: Focus on Infections and Malignancy. *Drug Dev Res*. 2015;76(8):419-427

45.- Haynes K, Beukelman T, Curtis JR, et al. Tumor necrosis factor α inhibitor therapy and cancer risk in chronic immune-mediated diseases. *Arthritis Rheum*. 2013;65(1):48-58.

46.- Bernatsky S, Boivin JF, Joseph L, et al. Mortality in systemic lupus erythematosus. *Arthritis Rheum*. 2006;54(8):2550-2557.

47.- Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine*. 2003;82(5):299-308.

48.- Soforo E, Baumgartner M, Francis L, et al. Induction of systemic lupus erythematosus with tumor necrosis factor blockers. *J Rheumatol.* 2010;37(1):204-205.

49.- Aringer M, Smolen JS. The role of tumor necrosis factor-alpha in systemic lupus erythematosus. *Arthritis Res Ther*. 2008;10(1):202.

50.- Aringer M, Steiner G, Graninger WB, et al. Effects of short-term infliximab therapy on autoantibodies in systemic lupus erythematosus. *Arthritis Rheum*. 2007;56(1):274-279.

51.- Williams EL, Gadola S, Edwards CJ. Anti-TNF-induced lupus. *Rheumatology*. 2009;48(7):716-720.

52.- Picardo S, So K, Venugopal K. Anti-TNF-induced lupus in patients with inflammatory bowel disease. *JGH Open*. 2019;4(3):507-510.

53.- Charles PJ, Smeenk RJ, De Jong J, et al. Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trials. *Arthritis Rheum*. 2000;43:2383-2390

54.- Kruithof E, Van Den BF, Baeten D, et al. Repeated infusions of infliximab, a chimeric anti-TNFalpha monoclonal antibody, in patients with active spondyloarthropathy: one year follow up. *Ann Rheum Dis*. 2002;61:207–212.

55.- De Rycke L, Kruithof E, Van Damme, N et al. Antinuclear antibodies following infliximab treatment in patients with rheumatoid arthritis or spondylarthropathy. A*rthritis Rheum*. 2003;48:1015-1023

56.- Garcia-Planella E, Domenech E, Esteve-Comas M, et al. Development of antinuclear antibodies and its clinical impact in patients with Crohn's disease treated with chimeric monoclonal anti-TNFalpha antibodies (infliximab) *Eur J Gastroenterol Hepatol*. 2003;15:351-354

57.- Ferraro-Peyret C, Coury F, Tebib JG, et al. Infliximab therapy in rheumatoid arthritis and ankylosing spondylitis-induced specific antinuclear and antiphospholipid autoantibodies without autoimmune clinical manifestations: a two-year prospective study. A*rthritis Res Ther*. 2004;6:535-543

58.- Vermeire S, Noman M, Van Assche G, et al. Autoimmunity associated with anti-tumor necrosis factor alpha treatment in Crohn's disease: a prospective cohort study. *Gastroenterology*. 2003;125:32-39.

59.- Allanore Y, Sellam J, Batteux F, et al. Induction of autoantibodies in refractory rheumatoid arthritis treated by infliximab. *Clin Exp Rheumatol*. 2004;22:756-758

60.- Eriksson C, Engstrand S, Sundqvist KG, et al. Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF alpha. *Ann Rheum Dis*. 2005;64:403-407.

61.- De Rycke L, Baeten D, Kruithof E, et al. Infliximab, but not etanercept, induces IgM anti-double-stranded DNA autoantibodies as main antinuclear reactivity: biologic and clinical implications in autoimmune arthritis. *Arthritis Rheum*. 2005;52:2192-2201

62.- Sellam J, Allanore Y, Batteux F, et al. Autoantibody induction in patients with refractory spondyloarthropathy treated with infliximab and methotrexate. *Joint Bone Spine*. 2005;72:48–52

63.- Atzeni F, Ardizzone S, Sarzi-Puttini P, et al. Autoantibody profile during short-term infliximab treatment for Crohn's disease: a prospective cohort study. A*liment Pharmacol Ther*. 2005;22:453-461

64.- Comby E, Tanaff P, Mariotte D, et al. Evolution of antinuclear antibodies and clinical patterns in patients with active rheumatoid arthritis with longterm infliximab therapy. *J Rheumatol*. 2006;33:24–30

65.- Colombel JF, Loftus EV Jr, Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. *Gastroenterology*. 2004;126:19–31

66.- Aghdashi MA, Khadir M, Dinparasti-Saleh R. Antinuclear Antibodies and Lupus-like Manifestations in Rheumatoid Arthritis and Ankylosing Spondylitis Patients at 4 Months' Follow-up After Treatment with Infliximab and Etanercept. *Curr Rheumatol Rev*. 2020;16(1):61-66.

****Overview of changes in antinuclear antibodies and lupus-like manifestations in patients on infliximab and etananercept.**

67.- Petri M, Orbai AM, Alarcón GS et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum*. 2012;64(8):2677-2686.

68.- Jani M, Dixon WG, Chinoy H. Drug safety and immunogenicity of tumour necrosis factor inhibitors: the story so far. *Rheumatology*. 2018;57(11):1896-1907.

****Review of safety of anti-TNF-alpha biologics.**

69.- Arnaud L, Mertz P, Gavand P, et al. Drug-induced systemic lupus: revisiting the ever-changing spectrum of the disease using the WHO pharmacovigilance database. *Annals of the Rheumatic Diseases.* 2019;78:504-508.

70.- Vaglio A, Grayson PC, Fenaroli P, et al. Drug-induced lupus: Traditional and new concepts. *Autoimmun Rev*. 2018;17(9):912-918.

71.- Ramos-Casals M, Brito-Zerón P, Muñoz S, et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Medicine*. 2007;86(4):242-251.

72.- Atzeni F, Talotta R, Masala IF, et al. Central nervous system involvement in rheumatoid arthritis patients and the potential implications of using biological agents. *Best Pract Res Clin Rheumatol*. 2018;32(4):500-510.

73.- Kemanetzoglou E, Andreadou E. CNS Demyelination with TNF-α Blockers. *Curr Neurol Neurosci Rep*. 2017;17(4):36.

74.- Jarvis B, Faulds D. Etanercept: a review of its use in rheumatoid arthritis. *Drugs* 1999;57:945-966.

75.- Markham A, Lamb HM. Infliximab: a review of its use in the management of rheumatoid arthritis. *Drugs* 2000;59:1341–1359

76.- Yazdani R, Simpson H, Kaushik V. Incidence of cytopenias in anti-TNF-α therapy [abstract]. *Rheumatology*. 2007;46:i33

77.-Wenham C, Gadsby K, Deighton C. Three significant cases of neutropenia with etanercept [letter]. *Rheumatology.* 2008;47:376–377

78.- Kuruvilla J, Leitch HA, Vickars LM, et al. Aplastic anemia following administration of a tumor necrosis factor-alpha inhibitor. *Eur J Haematol*. 2003;71(5):396-398

79.- Brunasso AM, Massone C. Thrombocytopenia associated with the use of anti-tumor necrosis factor-alpha agents for psoriasis. *J Am Acad Dermatol*. 2009;60(5):781-785.

80.- Michelmann I, Böckmann D, Nürnberger W, et al. Thrombocytopenia and complement activation under recombinant TNF alpha/IFN gamma therapy in man. *Ann Hematol.* 1997;74(4):179-184.

81.- Aster RH, Curtis BR, McFarland JG, et al. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. *J Thromb Haemost*. 2009;7(6):911-918.

82.- Bessissow T, Renard M, Hoffman I, et al. Review article: non-malignant haematological complications of anti-tumour necrosis factor alpha therapy. *Aliment Pharmacol Ther*. 2012;36(4):312-323.

83.- Haugaard JH, Kofoed K, Gislason G, et al. Association Between Drug Use and Subsequent Diagnosis of Lupus Erythematosus. *JAMA Dermatol*. 2020;2:e202786.

84.- Rubin RL. Evolving and expanding scope of lupus-inducing drugs. *Ann Rheum Dis*. 2019;78(4):443-445.

85.- He Y, Sawalha AH. Drug-induced lupus erythematosus: an update on drugs and mechanisms. *Curr Opin Rheumatol*. 2018;30(5):490-497.

**<u>TABLE 1:</u> Main reported studies of TNF alpha blockade in SLE**

| REFERENCE | Patients (n) | ANTI-TNF-alpha | CLINICAL FEATURES OF PATIENTS | CLINICAL EFFECTS OF ANTI-TNF- alpha | EFFECTS ANTI-TNF- alpha ON LABORATORY PARAMETERS | SLEDAI PRE anti-TNF-alpha | SLEDAI POST anti-TNF-alpha | MAIN ADVERSE EVENTS |
|---|---|---|---|---|---|---|---|---|
| [26] | 6 | Infliximab | • 4/6 : LN<br>• 3/6 : polyarthritis | ↓ Proteinuria: 6/6<br>Remission Arthritis: 3/3 | ↑ Anti-dsDNA in 4/6<br>IgM aCLP in 4/6<br>IgG aCLP in 1/6 | 9 | 5 | Infections (UTI) |
| [28] | 42 | Etanercept | • 35/42: arthritis<br>• 10/42: pleuropericarditis<br>• 6/42: SLS | • Arthritis remission: 35/35<br>• Serositis remission: 8/10<br>• ↑ FVC : 4/6 | ↑ Anti-dsDNA in 6/42 | - | - | Infections (UTI) |
| [30] | 15 | Etanercept (12)<br>Adalimumab (3) | • Arthritis | • Remission arthritis<br>• Improvement malar rash and alopecia | No increase observed | 6 | 0 | • Infections (septic arthritis, pneumonia)<br>• Neoplasia<br>• Myocardial infarction |
| [36] | 13 | Infliximab | • 9/13: NL<br>• 5/13: Arthritis | ↓ Proteinuria: 7/9<br>Remission Arthritis: 5/5 | NR | NR | NR | • Neoplasia<br>• Infections (UTI, pneumonia)<br>• DVT |
| [39] | 27 | Infliximab (9) | • Cutaneous, renal and/or joint involvement | • Overall improvement | ↑ ~ Anti-dsDNA (UI/ml)*: from 120.5 to 114.85<br>C3 (g/dl)*: from 0.51 to 0.92<br>C4 (g/dl)*: from 0.07 to 0.18 | 34.7 | 7 | NR |
| [50] | 7 | Infliximab | NR | NR | ↑ Anti-dsDNA: in 5/7<br>IgM aCLP: in 4/7<br>* levels NR | - | - | NR |

*SLE = Systemic lupus erythematosus; TNF = tumor necrosis factor; NR = Not reported; LN = lupus nephritis; SLS = shrinking lung syndrome. UTI = Urinary tract infection. DVT = Deep vein thrombosis*

Observed changes marked with an *****, were non significative.