
Infections and treatment of patients with rheumatic diseases

F. Atzeni¹, K. Bendtzen², F. Bobbio-Pallavicini³, F. Conti⁴, M. Cutolo⁵,
C. Montecucco³, A. Sulli⁵, G. Valesini⁴, P. Sarzi-Puttini¹

¹Rheumatology Unit, L. Sacco Hospital, Milan, Italy;

²Institute for Inflammation Research (IIR), Rigshospitalet and BioMonitor, Copenhagen, Denmark;

³Chair and Division of Rheumatology, IRCCS S. Matteo Foundation, University of Pavia, Italy;

⁴Department of Clinical Medicine and Medical Therapy, Chair and Unit of Rheumatology, Sapienza University of Rome, Italy;

⁵Research Laboratory and Academic Clinical Unit of the Rheumatology Department of Internal Medicine, University of Genoa, Italy.

Fabiola Atzeni, Klaus Bendtzen, Francesca Bobbio-Pallavicini, Fabrizio Conti, Maurizio Cutolo, Carlomaurizio Montecucco, Alberto Sulli, Guido Valesini, Piercarlo Sarzi-Puttini.

Please address correspondence to:
Piercarlo Sarzi-Puttini, MD,
Rheumatology Unit, L. Sacco University Hospital, Via G.B. Grassi 74, 20157 Milano, Italy.

E-mail: sarzi@tiscali.it

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ABSTRACT

Glucocorticoids (GCs) have many complex quantitative and qualitative immunosuppressive effects which induce cellular immunodeficiency and increase host susceptibility to various viral, bacterial, fungal and parasitic infections. As cortisol secretion is inadequate in chronic immune/inflammatory conditions, and current therapies have the aim of providing adequate (low) compensatory doses, the timing of GC administration, such as during the nocturnal turning-on phase of tumour necrosis factor (TNF) secretion, can be extremely important. The use of the lowest possible GC dose, at night, and for the shortest possible time should therefore greatly reduce the risk of infections. Infection is a major comorbidity in rheumatoid arthritis (RA), and conventional disease-modifying anti-rheumatic drugs (DMARDs) can increase the risk of their occurrence, including tuberculosis. TNF- α plays a key role in the pathogenesis of RA, and the data concerning infections in RA patients treated with anti-TNF agents are controversial. Patients and physicians should vigilantly monitor for signs of infection when using anti-TNF agents. Recombinant gene technologies now make it possible to produce protein drugs that are almost identical to naturally occurring human polypeptides, including antibody (Ab) constructs; unfortunately, all human biological agents are potentially immunogenic.

An increasing number of recent studies have demonstrated the safety of influenza and pneumococcal vaccines administered to patients with systemic lupus erythematosus (SLE) or RA. These vaccinations are generally immunogenic (i.e., capable of inducing a protective level of specific antibodies) but may not induce an adequate response in a substantial proportion of patients.

Introduction

Rheumatic diseases are associated with a number of immunological alterations and may themselves predispose to infections. A number of studies have reported an increased risk of infection in patients with rheumatic diseases compared to general population. For example, in rheumatoid arthritis (RA) patients the most frequent infections involve the musculoskeletal system, skin, subcutaneous tissues, and genitourinary and respiratory tracts (1, 2). Therapy with corticosteroids, conventional disease-modifying anti-rheumatic drugs (DMARDs) and biological agents can play an additional role in increasing the risk of infections.

In order to decrease the risk of infections in patients with rheumatic diseases, vaccinations have been proposed. However, the use of vaccinations in these patients is still a matter of debate due to the controversy regarding their efficacy and safety.

This review is focused on the risk of infections due to various anti-rheumatic drugs and on the efficacy/safety profile of some vaccinations.

Glucocorticoids

Glucocorticoids (GCs) have many complex quantitative and qualitative immunosuppressive effects that induce cellular immunodeficiency and increase host susceptibility to various viral, bacterial, fungal and parasitic infections (3). These effects have been seen at the cortisol levels typically encountered in patients with endogenous Cushing's syndrome, as well as at the GC levels achieved in patients receiving pharmacological concentrations. GCs exert their regulatory effects by transcriptionally upregulating or repressing specific genes: they first bind to and activate their cognate intracellular receptors and then, after translocating to the nucleus, the GC-receptor complexes modulate transcription by binding to specific elements within target-gene promoter regions.

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In particular, it has been found that the transcription factor, nuclear factor B (NF- κ B), is involved in multiple gene induction as part of immune and inflammatory response processes. There is growing evidence that a number of the immunosuppressive and anti-inflammatory effects of GCs may be due to the inhibition of NF- κ B and other transcription factors (3). GCs affect virtually every cell type involved in immune and inflammatory responses.

Chronic inflammatory conditions are characterised by inefficient endogenous GC production (4), and most of the mechanisms involved, such as decreased monocyte function, rapidly subside when GC treatment is interrupted; an observation that may explain the lower infectious risk associated with the use of short-acting GCs and alternate day treatments (5). The risk of infection increases with the dose and duration of treatment, and tends to remain low in patients exposed to low doses, even if the cumulative dose is high (6). More specifically, the risk associated with GC therapy depends on the route of administration and the potency of treatment. Furthermore, the host's underlying disease state, which dictates the dose and duration of treatment, largely contributes to the variability of infectious risk in clinical practice.

Restricting GC administration to less than 21 days might reduce infectious complications as it has been suggested that opportunistic infections rely on the prolonged suppression of T-lymphocyte-mediated cellular immunity (7). Consequently, using the lowest possible GC dose for the shortest possible time should decrease the risk of infection.

A meta-analysis of 71 trials involving more than 2000 patients with different diseases receiving different doses of GCs found a relative risk of infection of 2.0 (8). Five of these trials involved patients with rheumatic diseases and showed no increased relative risk. Two studies specifically involving patients with RA found that the incidence of serious infections was similar to that of placebo, or only slightly increased (9). The increased mortality observed in patients with RA is partly due to the

greater occurrence of serious infections. A retrospective study from the Mayo Clinic found that RA patients are at increased risk of infection, and that serious infections were associated with severe disease and the use of GCs.

The risk of infection leading to hospitalisation and the possible factors associated with this risk have very recently been examined in a prospective cohort study of 2108 unselected patients with new-onset inflammatory polyarthritis from a community-based register in whom the incidence of infection was compared with that observed in the local population (10). The patients were followed up annually for a median 9.2 years, and the contribution of potential predictors of the rate of hospitalisations for serious infection was assessed by means of a within-cohort analysis. The overall incidence of infection was more than two and a half times that of the general population (although it varied by site), and the significant independent predictors were a history of smoking, rheumatoid factor and the use of GCs; furthermore, the patients all three factors were more than seven times as likely to be hospitalised than the rest of the cohort. Unfortunately, no data were given concerning the doses of the GCs. These findings provide background data on the risk of infection associated with RA, and are of particular interest given the current awareness of the risk of infection associated with anti-tumour necrosis factor alpha (anti-TNF- α) treatments.

In patients treated with GC, physicians should anticipate the risk of infections due to both usual and unusual organisms, and bear in mind that GCs may blunt classic clinical features and delay the diagnosis. Under special clinical circumstances, and in severely immunocompromised patients, it may be wise to screen for latent infections such as tuberculosis, or institute prophylactic chemotherapy. *Pneumocystis carinii* infections deserve special attention because, in one series, prednisone doses of as little as 16 mg/day for eight weeks were associated with an increased risk. GC-treated patients should be immunised with standard vaccines such as influenza vaccines, although their

protective effect may be reduced. Live vaccines, including those against BCG, measles, rubella and chicken pox, are contraindicated.

As cortisol secretion is inadequate in chronic immune/inflammatory conditions, and current therapies have the aim of providing adequate (low) compensatory doses, the timing of GC administration, such as during the nocturnal turning-on phase of tumour necrosis factor (TNF) secretion, can be extremely important (4). The use of the lowest possible GC dose, at night, and for the shortest possible time should greatly reduce the risk of infections.

The correct management of GC in rheumatic diseases has been summarized in the recent guidelines published by the EULAR Task Force (11, 12).

Disease-modifying anti-rheumatic drugs

RA therapy with conventional DMARDs can increase the risk of infections, including tuberculosis (TB) (13), but only a few studies have been carried out in an attempt to ascertain the relevance of the role of different DMARDs.

At the low doses used in RA patients, methotrexate (MTX) seems to inhibit T cell activation and granulocyte function. A number of reports suggest an increased risk of infection during MTX therapy, but very few controlled clinical studies have considered this aspect. Van de Veen *et al.* (14) investigated the frequency of bacterial infections in RA patients treated with MTX and compared it with that observed in patients treated with other DMARDs (including hydroxychloroquine, sulphasalazine, gold, penicillamine and azathioprine) or who had never received a DMARD, and found that the overall infection rate and use of antibiotics was slightly higher in the MTX-treated group than in either of the other groups. The most frequent infections associated with MTX involved the skin and upper respiratory tract, but there was no increase in serious infections leading to drug withdrawal. Unlike previous reports indicating that MTX-treated patients with long-lasting RA show an increased rate of herpes zoster (HZ) infection, a

recent study did not find any difference between DMARD-treated RA patients (57% taking MTX) and patients with non-inflammatory musculoskeletal disorders (15). Jekes *et al.* (16) have recently investigated the frequency of infections in RA patients during treatment with leflunomide alone or in combination, and found that the overall infection rate was 3.3/100 patient-years and higher in patients with severe disease taking combined MTX and corticosteroid therapy. Wolfe *et al.* (17) have reported a relationship between the risk of pneumonia and leflunomide use in RA, whilst no increased risk was found with sulphasalazine or MTX.

There are few data concerning DMARDs other than MTX or leflunomide. The discontinuation of cyclosporine A, gold salts, sulphasalazine and hydroxychloroquine is mainly related to adverse events other than infections (18-20).

Anti-TNF agents

TNF- α not only plays a key role in the pathogenesis of RA, but also in host defence mechanisms (21), which may be important with regard to intracellular infections. Clinical trials of anti-TNF agents (infliximab, etanercept and adalimumab) have shown that they are effective in patients with severe RA, but some concerns have been raised concerning the general risk of infection. Some studies have found no difference between active treatment and placebo groups, but others suggest there may be an increased risk, and a few have found that this is statistically significant (21).

Pre-registration studies of TNF antagonists revealed 15 cases of TB among approximately 8000 treated RA patients, but passive surveillance studies indicate a higher incidence. Three reviews of the adverse events database have revealed an increased risk of TB, the predominance of atypical TB presentations (extra-pulmonary involvement and disseminated disease), and the re-activation of latent TB in anti-TNF-treated patients (21, 22). Consequently, all patients should be screened for latent TB by means of history, a physical examination, and purified

protein derivative (PPD) skin tests, and those with a positive PPD test (with or without positive chest radiography) and without any evidence of active disease should be started on single-agent treatment with, for example isoniazid (INH), before being given anti-TNF therapy (23-25).

Recent studies suggest that TNF- α may be involved in the pathogenesis of hepatocyte destruction in chronic HCV, and indicate that anti-TNF therapy may be safe and even beneficial (26); however, these data are very preliminary, and considerable caution is required when considering the use of anti-TNF treatment. Furthermore, animal studies have shown that TNF- α may also play a role in clearing or controlling HBV, and case reports indicate that the combination of infliximab and MTX re-activates chronic HBV infection (26). It is therefore recommended to screen all patients for hepatitis B before administering anti-TNF therapy by measuring hepatitis B surface antigen, hepatitis B surface antibody and hepatitis B core antibody, and patients with chronic hepatitis B should only use anti-TNF therapy together with an antiviral hepatitis B treatment such as lamivudine (21, 26).

Some studies have found that serious infections occur more frequently in association with TNF-blocking agents than with other DMARDs, but others have found no differences (21). Salliot *et al.* (27) examined 707 patients with infections occurring before or during anti-TNF therapy, and found that the serious infection rate was 2.9 ± 35 per 100 patient-years before and 8.8 ± 78 per 100 patient-years during therapy ($p = 0.02$). Kroesens *et al.* (28) studied 60 patients and reported an infection rate of 0.08 infections/year before and 0.181 infections/year after starting TNF blockers.

A meta-analysis by Bongartz *et al.* (29) showed that the risk of serious infections was twice as high (OR 2.0; 95% CI 1.3-3.1) in patients treated with anti-TNF agents than in DMARD-treated controls. A national prospective observational study of 7,664 anti-TNF-treated and 1,354 DMARD-treated patients with severe RA from

the British Society for Rheumatology Biologics Register (30) reported 525 serious infections in the anti-TNF cohort and 56 in the DMARD cohort after respectively 9,868 and 1,352 person-years of follow-up. The incidence rate ratio (IRR), adjusted for baseline risk, was 1.03 (95% CI 0.68-1.57) in the anti-TNF cohort, but the frequency of serious skin and soft tissue infections was much higher, with an adjusted IRR of 4.28 (95% CI 1.06-17.17); there was no difference in infection risk between the three main anti-TNF drugs. The same conclusion was drawn by the Swedish Arthritis Treatment Group that reported a non-significant relative risk ratio for severe infections (0.89-1.15) (31); the German Biologics Registry found that the relative risk ratio for serious infection was approximately 2.1 (32).

A study involving a large cohort of RA patients aged > 65 years found no increase in serious bacterial infections among those receiving anti-TNF therapy in comparison with those receiving MTX (33). However, the use of glucocorticoid use doubled the rate of serious bacterial infections in comparison with MTX, regardless of previous DMARD use (rate ratio (RR) 2.1 (95% CI 1.5-3.1), with a clear dose-response relationship for doses of > 5 mg/day: RR 1.34 for ≤ 5 mg/day; 1.53 for 6-9 mg/day; 2.97 for 10-19 mg/day; and 5.48 for ≥ 20 mg/day (p for trend <0.0001) (33).

The data concerning infections in anti-TNF-treated RA patients are controversial, but physicians and patients should vigilantly watch for signs of infection when using anti-TNF agents.

Biological agents in infections and autoimmunity

Using recombinant gene technologies, it is now possible to produce protein drugs that are almost identical to naturally occurring human polypeptides, including antibody (Ab) constructs. Many physicians have assumed that these may be administered with little or no risk of triggering specific T and/or B lymphocyte reactivities, believing that patients immunologically tolerate their own proteins; unfortunately, this is not

the case and even the so-called 100% human biologicals are potentially immunogenic (34, 35). We shall here discuss two groups of biopharmaceuticals: 1) recombinant human cytokines, exemplified by interferon (IFN)- β ; and 2) recombinant anti-cytokine Abs, exemplified by anti-TNF- α Ab constructs.

1. Recombinant human IFN- β drugs

IFN is a group of natural proteins produced by many cell types in response to challenges by infectious agents, primarily viruses. Natural, partly purified IFN preparations have been used for many years, primarily as therapies against viral infections and certain cancers but, since the 1980s, recombinant gene technologies have allowed mass cultivation and purification from bacterial and mammalian cell cultures.

IFN- β has been used to treat patients with multiple sclerosis (MS) since the early 1990s but, although initially neglected as a clinical problem, it is as immunogenic as many other 'human' proteins. The reported frequencies and titres of anti-IFN- β Abs vary considerably depending on the IFN- β preparations and administration, and the types of Ab assays (34, 36, 37).

It was more than ten years before the Ab-mediated decrease in IFN- β bioactivity (a condition in which the clinical effect of continued IFN- β injections is minimised or abrogated) was universally recognised (38). This was mainly due to the belief that the immune system tolerates peptides containing sequences that are identical or almost identical to their naturally occurring counterparts, but recognition of the problem was also delayed by the relapsing-remitting nature of MS and the use of inappropriate tests for anti-IFN- β Abs (34). It is now well known that up to 90% of treated MS patients develop Abs against IFN- β (36). However, the frequency and clinical relevance of these Abs depend on the nature of the drug as well as on treatment characteristics such as dosage and mode of administration. The assay format also greatly influences the frequency of Ab-positive patients (36, 37).

There are significant difficulties in obtaining reliable methods for monitoring

patients on prolonged IFN- β therapies. These include blood IFN- β analyses, which are required for optimal and individualised therapies, as well as methods of detecting the Abs induced during therapy (39). In an effort to assess the clinical relevance of *ex vivo* Ab measurements, many investigators distinguish 'binding' from 'neutralising' Abs, although this may not be clinically justified (34) as so-called non-neutralising binding Abs may affect drug bioavailability and clearance *in vivo*, and neutralising Abs may not necessarily neutralise circulating IFN- β *in vivo*. Moreover, anti-IFN- β Abs may cause serious complications and theoretically initiate autoimmune reactions whether or not they neutralize *in vivo*. Regular Ab screening and the discontinuation of therapy in MS patients with sustained high Ab levels are now generally recommended.

2. Recombinant humanised anti-TNF- α Ab constructs

TNF- α is a cytokine that is pathogenically important in many immunoinflammatory disorders, including infections and autoimmunity, and reducing its production or effects has long been a therapeutic goal.

Although two other anti-TNF- α biopharmaceuticals have shown promise in phase III trials, only three recombinant anti-TNF Ab constructs are currently approved for use in patients with chronic inflammatory diseases: 1) infliximab, a mouse-human IgG1-kappa anti-TNF- α monoclonal antibody; 2) etanercept, a fusion protein of human TNF receptor 2 and human IgG1; and 3) adalimumab, a fully human IgG1-kappa anti-TNF- α monoclonal Ab. All three greatly reduce disease activity and, in some patients, may induce remission.

However, not all patients respond favourably to anti-TNF Abs. Some do not respond at all (primary response failures), and others respond initially but experience relapses (secondary response failures) despite increased doses and/or more frequent administration. What causes these response failures is not clear, but individual differences in bioavailability and pharmacokinetics certainly make a contribution (40, 41).

Many clinicians, drug manufacturers and health authorities have paid little attention to this problem; furthermore, although drug delivery resembles otherwise effective vaccination procedures (repeated and, with some formulations, subcutaneous administrations of aggregated proteins), the immunogenicity of the drugs causing patients to develop anti-anti-TNF Abs has been largely neglected. It is therefore still not generally recommended to monitor patients for the development of anti-anti-TNF Abs.

Various methods have been used to assess circulating levels of anti-TNF drugs and anti-anti-TNF Abs, most of which have been based on enzyme-linked immunosorbent assay (ELISA) technology. There is little information concerning the *in vivo* relevance of these solid-phase assays, including their sensitivity, specificity and robustness (*e.g.*, are they affected by rheumatoid factors?); furthermore, standard ELISA techniques do not address the most clinically relevant factor of a drug's *in vivo* TNF- α binding capacity.

We have developed two fluid-phase radio-immunoassays (RIAs) to measure the functional blood and synovial fluid levels of the three marketed anti-TNF- α constructs and anti-anti-TNF Abs (all isotypes), and used them to monitor RA and inflammatory bowel disease (IBD) patients treated with infliximab and etanercept (40-41).

An increasingly recognised problem raised by the prolonged use of biopharmaceuticals is individual variability in drug bioavailability/pharmacokinetics and the induction of Abs. Increased pharmacovigilance is necessary as biopharmaceutical treatments are major and very expensive parts of the current medical therapies of a large number of patients with chronic infections and autoimmune diseases. Growing awareness of the inadequacies of long-term therapies with IFN- β and anti-TNF- α drugs has raised concerns as to whether it is justified to 'inoculate' patients for extended periods of time without monitoring them for Ab responses, or whether it is ethically correct to deprive patients of other (effective) therapies while treatment is continued in patients harbouring anti-drug Abs.

Vaccinations

Infectious diseases are frequent causes of morbidity and mortality among rheumatic patients who may be immunocompromised by the immunological dysfunctions of the disease or drug therapy (42). Whether or not patients with rheumatic disorders should receive vaccinations is a controversial issue among rheumatologists. Most of the data against the use of vaccines come from reported cases of previously healthy subjects who presented the onset of rheumatic disease after vaccination, suggesting the vaccine may have triggered a persistent autoimmune response in genetically predisposed subjects, such as IgA deficit, hypocomplementemia or specific HLA-DR (the "hit and run theory") (43). However, case reports are inadequate to support a causal link between immunisation and rheumatic diseases, which would require large-scale prospective studies, and genetic studies are also necessary in order to ensure safer vaccinations.

Systemic lupus erythematosus (SLE)

Over the last 20 years, there has been a marked improvement in the survival rate of SLE patients, but major infections probably remain the most frequent cause of death. SLE patients present several conditions that predispose them to infections: altered phagocytic cell activity involving neutrophils, lymphopenia, decreased cytokine production, low immunoglobulin levels, complement receptor abnormalities, acquired or inherited complement deficiency, and functional asplenia (44). SLE therapy *per se*, which is based on GCs and immunosuppressors, may favour infection processes, although GC modulation of the altered immune system and may actually improve its function.

SLE and influenza vaccination

Since 1978, a number of studies have examined the risk/benefit ratio of influenza vaccination in a total of 265 immunised SLE patients (45), and the data coming from one randomised, placebo-controlled, double-blind study, eight controlled studies, and one retrospective study indicate the safety of influenza vaccinations. With regard to

immunogenicity, the seroconversion rate in SLE patients is quite similar to, or slightly lower than that observed in normal subjects, but a considerable proportion of patients develop protective serum antibody serum levels.

SLE and pneumococcal vaccination

Encapsulated bacteria such as pneumococci, *Haemophilus influenzae* and meningococci are the leading infective agents in patients with abnormal humoral immune responses, such as those with SLE (44). Pneumococcal infections are common, and patients whose SLE is complicated by nephrotic syndrome, functional asplenia and hypocomplementaemia run the risk of developing fulminant pneumococcal infection.

In the late 1970s, the general view of preventive medicine and the finding that influenza vaccine was safe in SLE patients, encouraged investigators to assess the safety and immunogenicity of pneumococcal vaccination. Six studies have so far been published: two randomised double-blind controlled studies, three controlled studies, and one uncontrolled study involving a total of 250 immunised patients (46). Their overall results suggest that SLE patients can be safely and successfully immunised against pneumococcus, although the rate of seroconversion is lower than in normal subjects.

Rheumatoid arthritis (RA)

A number of studies have reported increased mortality associated with infection in RA patients. It has been estimated that the risk of developing an infection is almost twice as high in RA patients as in age- and gender-matched subjects (47). GC therapy may contribute to the development of infections, and controversial results have been reported concerning the influence of DMARDs (48).

RA and influenza vaccination

Seven studies (one double-blind randomised multicentre study, one randomised study, four controlled studies, and one retrospective study) have so far investigated the safety and immunogenicity of influenza vaccinations in

a total of 513 immunised RA patients (46-48). The results have shown that the vaccinations are safe and immunogenic in most cases, and the humoral response of RA patients does not seem to be affected by the use of prednisone, DMARDs or TNF- α blockers.

Oren *et al.* (50) have evaluated the effect of anti-CD20 monoclonal antibody (rituximab) on the immunogenicity and safety of influenza vaccination in RA patients. Vaccination was not associated with any significant worsening in any clinical or laboratory indices of disease activity and, in terms of immunogenicity, the vaccine generated an appreciable humoral response, although it was less than that observed in the patients not receiving rituximab or the healthy controls.

RA and pneumococcal vaccination

Five studies have recently assessed the safety and the immunogenicity of pneumococcal vaccination in 580 immunised RA patients (46, 47, 51). The vaccine was well tolerated and induced statistically significant humoral responses, although a substantial proportion of the patients responded poorly. Patients receiving concomitant methotrexate were less likely to respond to pneumococcal vaccination, but TNF- α blocking therapy did not seem to diminish the antibody response.

In conclusion, anti-influenza and anti-pneumococcal vaccines have proved to be safe in SLE and RA patients. In terms of immunogenicity, they are generally serologically effective, although the rate of seroconversion is lower than that observed in normal subjects.

The safety and efficacy of tetanus toxoid and anti-hepatitis B virus vaccinations have not yet been defined in these patients.

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