Review

Varicella-zoster virus infection in rheumatoid arthritis patients in the anti-tumour necrosis factor era

F. Cacciapaglia[1], C. Zuccaro[2], F. Iannone[3]

[1]Internal Medicine Unit, Rheumatology Outpatient Clinic Ninetto Melli Hospital San Pietro Vernotico, Italy;
[2]Geriatric Unit, Rheumatology Outpatient Clinic, Antonio Perrino Hospital, Brindisi, Italy;
[3]Department Interdisciplinary of Medicine, Rheumatology Unit, University of Bari, Bari, Italy.

Fabio Cacciapaglia, MD, PhD
Carmelo Zuccaro, MD
Florenzo Iannone, MD, PhD, Assoc. Prof.

Please address correspondence to:
Fabio Cacciapaglia, MD, PhD,
Internal Medicine Unit,
Rheumatology Outpatient Clinic,
Ninetto Melli Hospital,
Via Lecce 246,
72027 San Pietro Vernotico (BR), Italy.
E-mail: f.cacciapaglia@unicampus.it

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ABSTRACT

Patients with rheumatoid arthritis are increasingly being treated with different drugs (both non-biologic and biologic disease-modifying anti-rheumatic drugs – DMARDs) that may have immunomodulatory, cytotoxic, or immunosuppressive effects; in particular, anti-tumour necrosis factor (TNF) agents are raising major concern as regards safety issues. An increased risk of infections has been extensively reported during anti-TNF treatment, owing to the primary role of TNF in host defense and immune responses. Although in clinical practice cases of reactivation of varicella zoster virus (VZV) infections during therapy with TNF inhibitors commonly occur, the knowledge on this topic deriving from randomised clinical trials is limited. In this narrative review we focus on the pathophysiology of VZV infection and the role of TNF, and report the available data about VZV outbreaks recorded on Registries of rheumatic patients treated with anti-TNF agents. Finally, we discuss screening strategies and promising preventive measures against VZV infection.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder with systemic involvement that principally affects synovial joints, causing a substantial loss of function and mobility if not adequately treated (1). The course of chronic inflammation has been greatly modified by an earlier use of immunosuppressive agents and the relatively recent introduction of biologic drugs that temper the autoimmune response (2).

Biologic drugs used in the treatment of rheumatic diseases include different agents with specific immunological targets. Tumour necrosis factor alpha (TNF-α) is a pivotal cytokine in the pathogenesis of RA, and the inhibition of this factor is believed essential in the strategy of treatment of the disease. This can be achieved using monoclonal antibodies (infliximab, adalimumab, and golimumab), a dimeric Fc-TNF-receptor fusion protein (etanercept) or a pegylated Fab fragment of IgG (certolizumab pegol). These drugs, produced with molecular engineering techniques, have completely revolutionised the management of RA. There is evidence that patients treated early with anti-TNF therapies have less radiographic progression and a better functional outcome (3).

A major concern is the increased risk of infection due to the immunomodulation associated with the use of these drugs. In recent years, various reports have been published raising concern about infective safety issues in the course of anti-TNF treatment, varicella zoster virus (VZV) infection being the culprit in the majority of the reported infective events (4). The aim of the present narrative review is to analyse the pathophysiology of VZV infection and probe the role of TNF and of its inhibition, reporting the available data about VZV infections recorded on Registries of rheumatic patients treated with anti-TNF agents. Finally, possible therapeutic options and preventive strategies are outlined.

Rheumatoid arthritis and infection risk

Patients with RA have twice the risk of developing infective diseases as compared to non-RA subjects (5), and several factors increase this susceptibility. Firstly, when the immune system is engaged in an autoimmune response, as during RA, it must be considered basically deficient. Aberrations in the T cell repertoire, with the emergence of self-reactive oligoclonal populations, have been described in RA patients; thus, an altered CD4 T cell homeostasis may contribute to the autoimmune response, as well as to divert the im-

mune response, thus explaining the relative immunodeficiency observed in these patients (6). In RA, the severity of the autoimmune and inflammatory joint disease is correlated with large numbers of autoreactive $CD4^+CD28^-$ T cell-derived IFN-γ and TNF-α, which are scarce in healthy individuals. A profound dysregulation of the natural killer cell receptor NKG2D and its major histocompatibility complex (MHC) class I chain-related ligands may cause autoreactive T cell stimulation (7). Furthermore, RA patients have a markedly diminished T cell receptor function with ensuing aberration of T cell dynamics. Two models, not mutually exclusive, of thymic dysfunction and high T cell turnover can predict the compromised ability of RA patients to react against new antigens, as during infections (8). Moreover, in RA patients, differentiation defects and the inappropriate proliferation of T cells could contribute to the RA-associated immunosuppression and disease pathogenesis (9).

Other factors related to disease severity, advanced age, male sex, comorbidities, disease-modifying therapies and glucocorticoids use have been demonstrated to influence the susceptibility to infection of RA patients (10). A direct correlation has been reported between a greater disease activity and the likelihood of hospitalisation for serious infections (11). Moreover, the immunosuppressive therapy administered to control RA activity can increase the infection risk. In the past decade, a more aggressive approach to preventing RA damage and progression of the disability, featuring the extensive use of glucocorticoids and cytotoxic drugs (*i.e.* disease-modifying anti-rheumatic drugs – DMARDs) has reduced the inflammatory burden of the disease but has introduced a further latent safety risk related to the treatment itself (12).

Glucocorticoid therapy is strongly associated with an elevated, dose-dependent risk of non-serious and serious infections in RA patients. Current and/or recent doses of glucocorticoids have the greatest impact on infection risk (13, 14, 15), but the cumulative dose of the last 2–3 years also seems to be relevant (16). In contrast, the use of synthetic DMARDs, including methotrexate, does not seem to increase the risk of mild or serious infections, whereas the concomitant use of glucocorticoids is associated with a significantly increased risk of infection (17). Nevertheless, the long-term safety of these drugs is still uncertain, due both to the relatively small number of randomised clinical trials (RCT) long extended over 5 years, and to the use of combined therapeutic strategies (18). As regards herpes zoster (HZ) infection, a recent review (19) estimated an incidence ranging from 3.51 to 12.47 cases per 1,000 person-years in RA patients, with a 30% increased risk compared to the general population, and more frequently observed in patients with longer-term RA treated with DMARDs. HZ infection appeared to be self-limiting and curable (20), but literature data are conflicting (21). Wolfe *et al*. reported that in patients with RA and other non-inflammatory musculoskeletal disorders, the use of immunosuppressant drugs, but not methotrexate, was a significant predictor of HZ infection: multivariate analyses showed, for cyclophosphamide hazard ratio (HR) 4.2 (95% CI: 1.6–11.5), azathioprine HR 2.0 (1.2–3.3), leflunomide HR 1.4 (1.1–1.8) *versus* methotrexate HR 1.0 (0.8–1.3) (22).

The extensive use of TNF blockers to treat RA has raised awareness of the importance of safety (23). Anti-TNF drugs (24, 25, 26), owing to the main role of TNF in host defense and granuloma formation (27), are associated to an increased risk of opportunistic infections, including tuberculosis. Nevertheless, physicians should be aware of the risk of viral infection or reactivation during anti-TNF therapy (28). Clinical data that reflect the real use of anti-TNF in larger patient populations, that present different comorbidities and treatments without a suitable washout period, may aid in the evaluation of the real infection risk of RA patients who need to start or switch TNF inhibitors (29, 30).

Varicella-zoster virus (VZV) infection

Varicella-zoster virus (VZV) is a human alpha herpes virus of the *Varicellovirus* genus, recognised to be the causative agent of varicella (also known as chickenpox) as the primary infection, and zoster (also known as shingles) as a reactivation of previous infection (31).

Primary varicella infection is common, and usually with a favourable course, in children. However, disseminated varicella infection in adults, and especially in immune-impaired patients, can be severe and potentially fatal (32). In more than 95% of adults there is evidence of a prior VZV infection (33). In the European general population, the incidence of herpes zoster (HZ), caused by reactivation of VZV in sensory nerve roots varies by country, ranging from 2.0 to 4.6/1,000 person/years, with no clearly observed geographic trend (34). Patients with compromised cell-mediated immunity due to age, immunosuppressive agents, or concomitant illness have an increased risk of developing HZ (35). The severity of HZ is related to the degree of immune-competence, as also shown by the greater severity among patients with an organ transplant, lymphoproliferative diseases or the acquired immunodeficiency syndrome (AIDS). It has been noted that HZ is more common in patients with systemic lupus erythematosus (SLE) and RA, because of their impaired immune system as well as the medications used to treat these rheumatic diseases (36).

Epidemiological evidence suggests that primary VZV infection begins with viral replication in epithelial cells of the upper respiratory mucosa, followed by a wide distribution of the vesicular rash typical of varicella, after an incubation period of 10–21 days. This pattern probably reflects viral spread to the tonsils and other local lymphoid tissues, from which infected T cells can carry the virus via the bloodstream to the skin (37). During primary infection, virions presumably gain access to the sensory nerve cell bodies in ganglia by retrograde axonal transport from skin sites of replication or by T cell viraemia. Thus, latent infection can be established. When viral replication is reactivated, VZV reaches the skin via anterograde axonal flux to cause the symptoms of zoster, which is characterised by a vesicular rash in the dermatome innervated by the af-

fected ganglion. Both varicella and zoster skin lesions contain high concentrations of the infectious virus and are thus responsible for transmission to susceptible individuals (38).

VZV was initially classified as a neurotropic herpesvirus, but experiments using T cell xenografts in SCID mice *in vivo* and tonsil T cells *in vitro* showed that VZV also has T cell tropism (39). $CD3^+$ T cells, including $CD4^+$, $CD8^+$ and dual $CD4^+CD8^+$ T cell subpopulations, are fully permissive of the replication and release of infectious virions. VZV can infect tonsil T cells highly efficiently, suggesting that the virus is transferred from respiratory epithelial cells to T cells, presumably in the tonsils and other lymphoid tissues that comprise Waldeyer's ring, similarly to the transfer of the Epstein-Barr virus to tonsil B cells. VZV can also infect dendritic cells, which might facilitate the spread to lymph nodes. VZV-infected $CD4^+$ T cells predominantly show a memory T cell phenotype and express activation markers and skin-homing proteins, such as cutaneous leukocyte antigen (CLA) and CC-chemokine receptor 4 (CCR4), and are thus more likely to recirculate through the skin and other tissues. In addition, VZV induces activation and skin homing proteins on naive T cells (40).

TNF and the VZV infection

TNF and IL-1 are the early response cytokines of the innate immunity, and have pivotal biologic effects that may activate, amplify, and coordinate host responses to microbial challenges (41). TNF has a pleiotropic role in the activation and cross-talk between different immune system cells, so that an unbalanced concentration of this cytokine may change cell activation processes and the immune response. Data from *ex-vivo* and animal models used to evaluate immune function demonstrated that TNF signaling is essential to orchestrate innate immune activation as from the early phases of the acute inflammatory response. Neutrophil circulating numbers, migration and diapedesis are compromised in TNF receptor 1 (TNFR1) -deficient mice as compared to wild-type. Natural killer (NK) cells and dendritic cells (DCs) are essential effectors of the innate immune system that can rapidly recognise and eliminate microbial pathogens and abnormal cells, and induce and regulate adaptive immune functions. The TNF pathway is essential to activate the cell contact-dependent non-secretory apoptotic cytotoxic mechanism of NK and DC cells against infected cells, as well as virtually all types of cancer cells, and to regulate the cross-talk that leads to polarisation and reciprocal stimulation and amplification of Th1 type cytokines.

TNF exerts an antiviral activity, attributable to the direct killing of infected cells by the induction of FasL-dependent cytolytic T-lymphocyte effector pathways through the TNF/TNF receptor 2 interactions, as well as to indirect effects related to the role of TNF in promoting inflammatory responses. Moreover, it has been demonstrated that TNF stimulates VZV-specific immunoglobulin production and is capable of directly inhibiting the replication of VZV and its antigen expression. Finally, clinical studies have shown a decreased expression of the cytokines TNF and IL-6 in patients with more severe clinical manifestations during VZV infection, suggesting that measurement of intracellular levels of these cytokines could be a possible biomarker for the early identification of patients likely to have worse outcomes and hence candidates for a more careful management.

VZV and anti-TNF agents

Considered a relatively "benign" disease in children, but with potentially severe complications in adults and particularly immune-compromised individuals, who may show an atypical clinical presentation, herpes Zoster reactivation during anti-TNF treatment was firstly described in the Safety Trial of Adalimumab in Rheumatoid Arthritis (STAR Study) in 2003 (42) and other RCTs quote this infection as an uncommon event (3/1000 patient years) (43).

In routine clinical practice, the first case of disseminated primary varicella infection during anti-TNF treatment was reported in 2004 in a 26-year-old man with Crohn's disease (44). This patient developed primary varicella infection 9 days after starting infliximab treatment (3 mg/kg); the infection was complicated by hepatic failure and disseminated intravascular coagulation, resulting in cardiac, pulmonary and renal failure and death of the patient. The authors concluded that, given the severity of VZV in adults, the development of a vesicular rash in patients undergoing treatment with TNF inhibitors should be a signal for the immediate implementation of evaluations for VZV infections. Since then, different cases and retrospective studies have been published highlighting the increased risk of VZV infections in patients on anti-TNF therapy for inflammatory conditions, above all inflammatory bowel diseases. Among these, a peculiar clinical presentation was the one featuring a severe HZ in a 20-year-old man with Crohn's disease at the site of the 7^{th} and 9^{th} infusion of infliximab (45), while a case of disseminated HZ mimicking vasculitis occurred in a patient with RA on etanercept therapy (46). In 2009, McDonald *et al*. (47) reported 96 subjects with incident HZ among 3,661 RA patients undergoing anti-TNF treatment. Of these, 59 cases occurred in treatment with etanercept, 33 with infliximab, and only 4 with adalimumab. In this retrospective cohort study using the US Veterans Affairs Health system database, authors demonstrated an elevated incidence of herpes zoster in RA – 9.96 cases per 1,000 patient years. Correlates of HZ include older age, glucocorticoid use, traditional (methotrexate, leflunomide, azathioprine, cyclophosphamide, cyclosporine) and biologic DMARDs (anakinra and TNF blockers), malignancy, chronic lung disease, renal failure, and liver disease. Moreover, in 2011 Dreiher *et al*. (48) analysed the risk of HZ in a group of 22,330 psoriatic patients treated with systemic therapies: among the anti-TNF drugs, only the association with infliximab approached statistical significance for the risk of HZ, while no cases of HZ were seen among patients treated with adalimumab.

Overall, the majority of VZV infections was described in patients treated with TNF blockers and concomitant

immunosuppressive agents, such as MTX and azathioprine, for at least one month. The risk was further increased in female subjects, aged over 50 years, particularly if treated with monoclonal antibodies. In a recent study based on the Consortium of Rheumatology Researchers of North America (CORRONA) registry (49), VZV infection was the most frequent opportunistic infection, accounting for 44% of all cases, in patients taking methotrexate (MTX), TNF blockers or other DMARDs. The most important warning of an increased incidence of skin infections (including shingles) in RA patients under anti-TNF therapy came from the British Society for Rheumatology Biologics Register (BSRBR) (50). The crude incidence rate for all soft tissue and skin infections was 16/1,000 patient-years (95% CI: 14–18) in anti-TNF treated patients against 7/1,000 patient-years (95% CI: 5–10) in patients treated with non-biologic DMARDs. The incidence of HZ was 16/1,000 patient-years (95% CI: 13–20) in the anti-TNF group and 8/1,000 patient-years (95% CI: 6–11) in the non-biologic DMARDs group. After adjustment for age, gender, disease activity, comorbidities and treatment, in anti-TNF patients the HRs for all soft tissue and skin infections was 1.4 (95% CI: 0.9–2.4) and 1.8 (95% CI: 1.2–2.8) for shingles. Considering the different anti-TNF agents, no differences were found for soft tissue and skin infections, while for shingles the lowest risk was observed for adalimumab, with an adjusted HR of 1.5 (95% CI: 1.1–2.0), while the highest risk was observed for infliximab (HR 2.2; 95% CI: 1.4–3.4) considering as reference non-biologic DMARDs

Strangfeld *et al*. assessed the risk of VZV reactivation during treatment with anti-TNF, analysing data from the German biologics register "Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT)" (51). This prospective analysis showed a significant increased risk of HZ in patients receiving treatment with monoclonal antibodies – infliximab and adalimumab – (HR, 1.82, 95% CI: 1.05–3.15), even after adjusting for age, RA disease severity, and glucocorticoid use. Notably, no significant association was found for etanercept (HR 1.36, 95% CI: 0.73–2.55). Another study concluded that among the TNF blockers, etanercept (HR 0.62, 95% CI: 0.40–0.95) and adalimumab (HR 0.53, 95% CI: 0.31–0.91) appeared to pose a lower risk of HZ, compared to infliximab (HR 1.32, 95% CI: 0.85–2.03).

Data from the Spanish National Drug Safety Registry of patients with rheumatic diseases treated with biological agents (BIOBADASER) reported 907 episodes of infection, among 6,969 patients recruited from February 2000 to January 2006, with an observed incidence of 53 cases/1,000 patient-years (CI: 95%: 49.69–56.66). The most frequent infections were skin infection (12.18 cases / 1,000 patient-yrs), while VZV and Herpes simplex virus caused most cases of viral infections (52). In 2010, García-Doval *et al*. (53) performed a sub-analysis of data from the BIOBADASER and the National Hospital Discharge Database (*Conjunto Mínimo Básico de Datos al Alta Hospitalaria*) aimed at estimating the incidence of hospitalisation due to VZV infection in patients treated with TNF antagonists for rheumatic diseases, as compared to the expected rate in the general population. The authors reported an estimated incidence ratio (IR) of hospitalisation due to shingles in patients exposed to TNF antagonists of 0.32 cases per 1,000 patient-years (95% CI: 0.14–0.78), while the expected rate in the general population was not significantly different being 0.34 (95% CI: 0.32 –0.35). The standardised incidence ratio (SIR) was 9 (95% CI: 3–20) and the standardised incidence difference (SID) was 26 (95% CI: 14–37). The estimated IR of hospitalisation due to chickenpox was 0.26 cases per 1,000 (95% CI: 0.1–0.69), the expected rate was 0.19 (95% CI: 0.18–0.2), the SIR was 19 (95% CI: 5–47) and the SID was 33 (95% CI: 21–45).

In 2012, Atzeni *et al*. (54) reported results from the GISEA (Gruppo Italiano Studio Early Arthritis) Register on the risk of serious infections in 2,769 adult patients with long-standing RA during 9 years of treatment with the three anti-TNF agents licensed in Italy between 2001 and 2004 (infliximab, etanercept and adalimumab). Authors reported an incidence of serious infections in 31.8/1000 patient-years (95% CI 25.2–38.3), with a statistically significant difference among the three drugs: 65.1/1000 patient-years (95% CI 48.4–81.8) for infliximab, 23.7/1000 patient-years (95% CI 13.1–34.2) for adalimumab, and 12.8/1000 patient-years (95% CI 6.3–19.4) for etanercept. Hundred seventy-six patients experienced a serious infection and the most prevalent affected the upper and lower respiratory tract (50% of cases), followed by urinary tract infections (13% of cases) and skin infections (12% of cases), with HZ reactivation accounting for about half of the skin diseases. The application of multivariate models confirmed that the use of glucocorticoids (OR 1.633; 95%CI: 1.01–2.644), combination therapy of DMARDs and anti-TNF drugs (OR 2.14; 95%CI: 1.28–3.595), and older age at the start of anti-TNF treatment (OR 1.036; 95%CI: 1.02–1.053), were predictors of infection. Other factors independently associated with an increased risk of infection were the use of infliximab (OR 4.916; 95%CI: 2.71–8.906) or adalimumab (OR 2.22; 95% CI: 1.12–4.42; p=0.023) rather than etanercept.

Clinical trials are the gold standard to assess the efficacy of new medicines, but safety evaluation needs prolonged observation periods to be reliable. Furthermore, clinical trials are conducted in standardised conditions, far from the real world of prescription and use, and discrepancies in patient selection or treatment conditions may contribute to underestimate the rate of incident infections. Data from National registries of patients, with large sample size and long term follow-up, enables a better estimation of event rates with hard endpoints and outcomes, like the incidence of chickenpox and shingles in RA patients. On the other hand, variability in treatment, populations and settings with different time intervals between visits, represent relevant weaknesses and sources of bias and justify the divergent in results from Registry studies. In this regard, the striking difference in shingles incidence reported by the British

(16/1000 patients-years) and the Spanish (53/1000 patients-years) Registries, or a different risk of HZ reactivation with the different anti-TNF used, may be explained by surveillance bias, the different background use of systemic glucocorticoids in BIOBADASER (>80%) compared to UK (<40%), or different environmental conditions or preventive strategies and organisation of National Health Services.

Screening and preventive strategies

Due to their infection risk, the Societies of the physicians that use these drugs (Rheumatologists, Gastroenterologists and Dermatologists) drafted National clinical guidelines for screening, prophylaxis and critical information required prior to starting anti-TNF-alpha treatment, with evidence-based recommendations (55-57). All these include screening for both active and latent tuberculosis, as well as hepatitis B and C exposure/infection, and Human Immunodeficiency Virus (HIV) test. Some Societies advocate the screening also for Epstein Barr virus (EBV), Human Papilloma virus (HPV), Pneumococcal, fungal and parasitic infections.

Because VZV is a highly contagious disease, the American College of Rheumatology, the British Society of Rheumatology, the French Society of Paediatric Rheumatology, the Danish Society of Gastroenterology and Hepatology, and the European Crohn's and Colitis Organisation have paid particular attention to this risk, and recommend a careful collection of patient's history of previous infection and/or vaccinations before anti-TNF treatment. Moreover, patients should be advised to seek medical advice in cases of muco-cutaneous lesions attributable to VZV infection. The cost/benefit ratio needs to be taken into account in the evaluation for VZV infection. Most experts agree that information about VZV exposure and/or infection must be collected but a VZV antibody test should be performed only when VZV infection is uncertain. In patients without a prior VZV infection, VZV vaccination may be considered, as immunisation with the VZV vaccine is an effective approach to prevent both primary varicella infection and HZ.

Varicella epidemics occurred annually in the United States until a varicella vaccine was introduced in 1995. This vaccine is a single dose, high-potency, live, attenuated form of the VZV Oka strain, that boosts VZV-specific cell-mediated immunity. Evidence that the vaccine is effective in older patients was obtained in the pivotal Shingles Prevention Study (58), which demonstrated that the HZ vaccine significantly reduced morbidity due to zoster and post-herpetic neuralgia in older patients. However, the duration of efficacy beyond 5 years after vaccination remains unclear. In any case, being a live, attenuated vaccine, generally contraindicated in immune-compromised patients, the use of the VZV vaccine in RA is debated. The European league against rheumatism (EULAR) postulated that HZ vaccination might be considered in all patients with autoimmune inflammatory rheumatic diseases with no previous VZV infection, the level of evidence being III-IV and strength of recommendation C-D (59). The suggestion to avoid live vaccine whenever possible, in the case of HZ vaccination can be considered an exception to this rule for those patients on anti-rheumatic drugs who are mildly immunosuppressed, whom should be assessed on a case-by-case basis. Temporary discontinuation of immunosuppression may be considered, but there are no supporting evidences. If considered necessary, HZ vaccine should be administered only to patients who are seropositive for VZV antibodies in order to prevent varicella reactivation with the vaccine strain.

Epidemiological data demonstrated that patients suffering from rheumatic diseases exposed to TNF antagonists are hospitalised for VZV infections significantly more frequently than the expected rate in the general population. Observational studies (60, 61) have not demonstrated an increased risk of HZ in vaccinated patients on anti-TNF agents, but because the absolute incidence rate of hospitalisations due to VZV infection (both chickenpox and shingles) is low in these patients, the implementation of potentially risky preventive measures may not be justified until further evidence becomes available, and the advice to proceed cautiously when considering more potent immunosuppression remains valid. Vaccination guidance based on the type and intensity of immunosuppression would aid to unravel doubts and ensure a unified approach to patient care. Until an efficacious inactivated VZV vaccine will be available, physicians will continue to face the challenging decision whether or not to vaccinate their immune-compromised patients. If vaccination is decided upon, administration at least 2 weeks prior to immunosuppression where possible is advised. For those patients already on immunosuppressive drugs, the decision of vaccination should be discussed with the patient in a secondary care setting according to the individual risk. Finally, in the absence of National recommendations the appropriate management of patients who have been exposed to, or have developed VZV infection, during anti-TNF treatment is based on good clinical practice, mainly dictated by the pathophysiology of the virus infection and anti-infective strategies (62).

The cessation of biologic therapy in exposed, asymptomatic patients with no immune-impairment history or active infection is the strongest endorsement. More severe clinical manifestations of chickenpox, with multi-dermatomal shingles, cranial nerve involvement or shingles associated with fever, should be treated with *i.v.* antiviral drugs (acyclovir), while uncomplicated shingles can be treated with oral antiviral drugs up to 2 days after all lesions have crusted over. However, cases of acyclovir-resistant VZV infection have been reported (63). In exposed patients with no clinical manifestations, a serological immunity evaluation for the presence of VZV IgG should be urgently performed, and the administration of specific immunoglobulin (VZ-Ig) could be justified if antibodies are negative or if the results are expected late over one week post exposure. Finally, biologic treatment could reasonably be started 21 days after the last exposure if patients are asymptomatic.

Conclusion

Both disease conditions and medications can impair cell-mediated im-

munity and increase the risk of VZV infection. The rate of serious infections, and in particular those related to VZV during TNF blocker treatment, observed in daily practice settings, as reported by many Registries, is much higher than the rate observed in RCTs. Serious infections are frequent in daily practice and close monitoring and accurate patients selection are essential. Indeed, more than 30% of RA patients discontinue their first biologic drug within 1 year due to lack of efficacy and/or adverse events. In the event of a recent, serious adverse event, such as a hospitalised infection occurring while on anti-TNF therapy, the 2012 American College of Rheumatology recommendations (64) suggest switching to a non-anti-TNF biologic, but given the limited evidence of a correlation between serious infection and biologic therapies in high risk RA patients, this recommendation was based on level C evidence (expert opinion).

High risk patients should be preventively evaluated when clinicians decide to start biologic treatment or to switch to a different anti-TNF agent. Some tools are available to estimate the risk of individual patients to develop a serious infection, based on their clinical profile. In 2002, researchers from the Rochester cohort proposed a risk score considering different factors such as age, previous infection, comorbidity or glucocorticoid dose, and demonstrated that RA severity, functional status and comorbidity were predictors of serious infection. However, this score does not include considerations on treatment with biologic or non-biologic DMARDs (65). Another risk score for infections was developed in 2012 by Curtis *et al*. (66) using two administrative databases in the USA. Predictors of serious infection were older age, comorbid conditions, higher dosages of glucocorticoids and previous serious infections. Diabetes mellitus was also associated with a moderately increased risk, but parameters of RA disease activity or severity were not considered in this score. More recently, using data from the RABBIT patients cohort, a risk score for serious infections was proposed by Zink *et al*. (67). This risk score promises to be a reliable tool to determine the risk of serious infection during the next 12 months in individual patients based on clinical and treatment information. Parameters considered are age, HAQ-score, previous severe infections, comorbidities (lung or kidney impairment), treatment with non-biologic and/or biologic DMARDs and glucocorticoids dosages. The use of a tailored risk evaluation seems to be the best way to help rheumatologists to balance the benefits and risks of treatment, avoid high-risk treatment combinations and make informed clinical decisions. However it should be kept in mind that the proposed risk scores are not specific for VZV infections and should be further validated in different cohorts of patients. In conclusion, the increased risk of VZV infection in RA patients is caused by disease-related immune system dysregulation, further impaired by the immunosuppressive therapy, mainly glucocorticoids but also non-biologic and biologic DMARDs. Clinicians should always take into account all these elements during therapeutic decision-making.

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