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Incidence, Clinical Features, Management, and Prevention of Herpes Zoster in Patients Receiving Antitumor Necrosis Factor Therapy: A Clinical Review

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Abstract

Tumor necrosis factor (TNF) inhibitors have been used as an excellent therapeutic option in a variety of chronic inflammatory conditions. However, a recognized significant adverse effect of TNF inhibitor therapy is the increased risk of infections. The influence of TNF inhibitors on the course of coexisting or newly developed viral infections has not been extensively investigated. Therefore, we reviewed the recent publications to highlight the incidence, clinical features, management, and prevention of herpes zoster in patients who are receiving TNF inhibitors.

Keywords

herpes zoster, anti-TNF therapy, TNF inhibitors, TNF antagonists, vaccination, varicella zoster virus

Introduction

Herpes zoster (shingles) is an acute condition that may severely affect the quality of life of affected patients.¹ It results from the reactivation of latent endogenous varicella zoster virus (VZV) infection within the sensory ganglia. Infection may consist of a dermatomal involvement, and more rarely, the severe disseminated form of the disease.² It can substantially contribute to an element of morbidity, disability, or chronic pain in the form of postherpetic neuralgia (PHN).^{3,4}

Approximately 1 out of every 3 people in the United States will develop herpes zoster within their lifetime.^{5,6} Aging is the most important risk factor for herpes zoster, as it most commonly affects the elderly.⁶ Patients with immunosuppression, diabetes, systemic lupus erythematosus, rheumatoid arthritis (RA), psychological stress, mechanical trauma, psychiatric disease, organ transplant, and females are at higher risk of developing the disease.⁷

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine with multiple roles in the stimulation and regulation of the immune system. Primarily, it has detrimental effect on the course of chronic, immune-mediated inflammatory disorders.⁸

Tumor necrosis factor inhibitors including adalimumab, infliximab, golimumab, and certolizumab pegol (Fab

fragment of a monoclonal antibody), and etanercept (dimeric fusion protein) have proven highly effective in the induction and maintenance of remission of several chronic inflammatory diseases. However, due to the immunological properties of TNF, safety concerns regarding the development of severe bacterial infections and the reactivation of tuberculosis have been raised.³

Limited data exist about the effect of TNF inhibitors on the course of existing or newly developed viral infections. An *in vitro* study in human lung embryonic fibroblasts (HEL) showed that TNF- α activation completely blocked the

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replication and antigen expression of VZV.⁹ Therefore, patients receiving TNF inhibitors may suffer from primary varicella infection or reactivation of latent VZV.^{9,10}

There are various guidelines for the treatment and prophylaxis of herpes zoster, however, these may not be ideal for patients receiving TNF inhibitors. A clinician's awareness of management guidelines for the treatment and prevention of VZV infection is critical in minimizing the risk of the disease and the associated morbidity in the patient. Therefore, we present an overview of the recent data available on the risk of herpes zoster and its clinical features in a patient receiving anti-TNF (etanercept, adalimumab, and infliximab) therapy. We also address the management and preventive strategies for herpes zoster in patients treated with anti-TNF medication.

Search Methodologies for Preparation of the Article

For this review, we used PubMed to identify the publications on the incidence, clinical features, management, and prevention of herpes zoster in patients who are receiving TNF inhibitors. Our study included English articles published between 2010 and 2018. The following terms were used for the search of the literature: Herpes zoster, Anti-TNF therapy, TNF inhibitors, TNF antagonists, Vaccination, and Varicella zoster virus. No specific exclusions were set. All the references cited in those selected papers were also reviewed to identify additional studies not indexed by the PubMed. Online search yielded a total of 387 articles which were first reviewed for the titles and abstracts. After excluding 272 papers because they were not relevant to the topics of interest or focused on basic science or immunology topics, we finally included 58 clinical reports for this review.

Incidence of Herpes Zoster in Patients Receiving Anti-TNF Therapy

There is abundant literature concerning the risk of herpes zoster in patients with RA, inflammatory bowel diseases (IBD), and psoriasis, both with and without the use of TNF inhibitors. Furthermore, large retrospective databases and prospective clinical trials have provided evidence that therapy with TNF inhibitors was associated with an increased incidence of herpes zoster.¹¹⁻¹⁵ In fact, it has been reported that the incidence of herpes zoster in the general population ranges from 3.2 to 4.2 cases per 1000 person-years,¹⁶ while the incidence increases to 10.6 per 1000 patient-years in patients receiving anti-TNF therapy.¹⁷

In 2007, 4393 RA patients were included in a study utilizing German registry data to evaluate the episodes of herpes zoster.¹⁸ The incidence of herpes zoster was estimated to be 1.45% (64/4393) in patients treated with TNF inhibitors. Compared to those not receiving treatment, the infliximab- and adalimumab-treated groups were significantly

associated with the risk of herpes zoster. In contrast, the use of etanercept did not significantly increase the herpes zoster risk in patients. This difference persisted after adjustment for disease activity at treatment initiation.¹⁸ In the 2009 RABBIT study, analysis data from the German biologics registry demonstrated that anti-TNF monoclonal antibodies increased the risk of herpes zoster 2-fold in RA patients.¹⁹ They found that the incidence of herpes zoster (in per 1000 patient-years) in this population was 11.1 with both adalimumab and infliximab, 8.9 with etanercept, and 5.6 with conventional disease-modifying antirheumatic drugs. After adjustment for age, RA severity, and use of glucocorticoids, the risk was significantly higher for the group treated with monoclonal antibodies (hazard ratio [HR] = 1.82; 95% CI = 1.03-3.15) than for etanercept (HR = 1.36; 95% CI = 0.73-2.55).¹⁹ A study by Galloway et al showed similar results: a higher risk of herpes zoster was seen in patients with RA receiving TNF inhibitors than in those receiving conventional disease modifying antirheumatic drugs.¹³ A meta-analysis also revealed a significantly increased risk of herpes zoster (up to 61%) in RA patients receiving TNF inhibitors.²⁰

A retrospective study on chronic inflammatory joint diseases (RA, ankylosing spondylitis, etc.) detected 9 cases (3%) of herpes zoster among 300 patients exposed to TNF inhibitors. The mean exposure duration before the onset of herpes zoster was 27 months. In these 9 cases, 4 patients received infliximab, 2 received adalimumab, and 3 received etanercept (of these 3, 2 patients previously had received infliximab therapy).²¹

Furthermore, several prospective clinical trials on IBD have provided perspective on the effect of TNF inhibitor therapy on the development of herpes zoster.²² Colombel et al reviewed 6 major clinical trials studying adalimumab and was able to identify 46 cases (6 severe) of herpes zoster (1.46%) among 3160 Crohn's disease patients.²³ In a long-term safety report by Lichtenstein et al in 2012, the incidence of herpes zoster was 0.27 per 100 patient-years in the infliximab-treated Crohn's disease group, whereas the incidence was 0 per 100 patient-years in both the infliximab-treated ulcerative colitis and placebo groups.²⁴ According to another study, patients with Crohn's disease who received anti-TNFs had an elevated risk of herpes zoster as well as of subsequent PHN.²⁵

Contrary to other chronic inflammatory diseases, relatively limited data exist on studies assessing the risk of herpes zoster in patients with psoriasis.⁴ In 2011, Dreier et al investigated the risk of herpes zoster in 22330 psoriasis patients treated with systemic therapies including TNF inhibitor therapy.²⁶ In their study, among the TNF inhibitors, only infliximab was associated with an elevated incidence of herpes zoster. None of the other TNF inhibitors had a significant association with the development of herpes zoster. According to a Japanese study conducted by Umezawa et al, herpes zoster was observed in 1 out of 39 psoriasis patients receiving

infliximab and 3 out of 65 psoriasis patients receiving adalimumab within 1 year of treatment. None of the patients were receiving combination therapy with other immunosuppressive agents such as methotrexate or cyclosporine.²⁷ Their results were consistent with the earlier reports citing that the incidence of herpes zoster in psoriasis patients receiving TNF inhibitors were higher than that in the general population. A large population-based psoriasis study found no significant association between the use of biologic monotherapy and the onset of herpes zoster. However, the incidence of herpes zoster increased with the use of combination treatment with methotrexate and biologic agents (RR = 1.66; 95% CI = 1.08-2.57; $P = .02$).⁴

As described previously, the difference in the incidence of herpes zoster might depend on the specific TNF inhibitor used.^{18,20,26} A significant positive association was found between herpes zoster and treatment with monoclonal anti-TNF antibodies, especially infliximab; however, treatment with TNF receptor analog etanercept was not significantly associated with an increased risk of herpes zoster.²⁰ This finding was in agreement with the previous reports with composite endpoints showing higher infection rates with infliximab than with etanercept.²⁸⁻³⁰ According to a retrospective study by McDonald et al in 2009,¹⁷ RA patients receiving etanercept (HR = 0.62) and adalimumab (HR = 0.53) exhibited a lower risk of herpes zoster than RA patients receiving infliximab (HR = 1.32). Salmon-Ceron et al recently suggested that monoclonal anti-TNF antibody (rather than soluble TNF receptor etanercept) and steroid use (>10 mg/day orally or intravenous boluses within the past year) were independently associated with an increased risk of opportunistic infections (infliximab, odds ratio [OR] = 17.6; adalimumab, OR = 10.0).²⁸ Recently, another review showed higher herpes zoster incidence and severity in patients receiving monoclonal anti-TNF antibodies than in those receiving soluble TNF receptor (etanercept, OR = 1; adalimumab, OR = 3.25; infliximab, OR = 3.94).¹⁵

According to many reports, regardless of the underlying disease, infliximab seems to be associated with a higher risk of herpes zoster development^{13,15,26,31} than etanercept.^{32,33} Interestingly, even young patients who are not typically at risk for herpes zoster showed increased risk while receiving infliximab.³⁴

The differences in the risk of herpes zoster may be explained by different mechanisms and characteristics of different TNF inhibitors. In contrast to etanercept, infliximab induces cytotoxicity in TNF-expressing monocytes and T cells, inducing the expression of different leukocyte genes.^{34,35} Additionally, due to its pharmacokinetic properties, infliximab might be associated with a higher risk of herpes zoster than adalimumab, as infliximab is able to reach higher concentrations in tissue microenvironments.^{34,36}

A subset of patients treated with anti-TNF agents do not appear to have increased risk for herpes zoster.^{17,31,37} In

2009, Wolfe et al demonstrated patients with RA and noninflammatory musculoskeletal disorders within the National Data Bank for Rheumatic Diseases (NBD) registry had a higher risk of herpes zoster than the remaining population.³¹ However, methotrexate and TNF inhibitors (infliximab, adalimumab, and etanercept) were not found to be risk factors.³¹ Similarly, Winthrop et al found that patients with RA, IBD, psoriasis, psoriatic arthritis, and ankylosing spondylitis receiving TNF inhibitors were not at a higher risk for herpes zoster than the patients not receiving treatment with biologics.³⁷ Furthermore, no significant difference was detected in herpes zoster risk between decoy receptor etanercept and the monoclonal antibodies.³⁷ A large proportion of subjects were Medicare and Medicaid recipients or using concomitant immunosuppressives, which may have influenced these negative results.³⁷

Clinical Features of Herpes Zoster in Patients Receiving Anti-TNF Therapy

It has been reported that patients receiving TNF inhibitor therapy have an increased risk of herpes zoster; however, this VZV reactivation may result in a more severe and extensive disease involving multiple dermatomes, potentially requiring hospitalization.

According to the data reported by Strangfeld et al, 15 of 62 (24.2%) cases of herpes zoster that occurred during treatment with TNF inhibitors involved multiple dermatomes or ophthalmic zoster. Severity and duration of herpes zoster were also increased in patients receiving TNF inhibitors.¹⁹ Failla et al showed similar results: bidermatomal (45%) and multidermatomal (32%) herpes zoster cases were common in patients receiving TNF inhibitor therapy.³⁸ Galloway et al also reported that TNF-inhibitor treated patients tend to experience severe shingles (multidermatomal, requiring intravenous antiviral agents, or hospitalization).¹³ A Spanish study by Garcia-Doval et al revealed significantly more frequent VZV-related hospitalizations in patients exposed to TNF inhibitors than in the general population.³⁹ Furthermore, there are more reports of severe herpes zoster infections from randomized controlled trials and open-label follow-up studies involving TNF inhibitors.⁴⁰⁻⁴²

The timing of the onset of herpes zoster in patients receiving TNF inhibitors therapy is also not certain. Serac et al found increased risk of herpes zoster during initiation of TNF inhibitor therapy.¹⁵ Another report showed that 79% of herpes zoster cases occurred between 6 and 36 months after the start of immunosuppressive treatment.³³

There are conflicting results for PHN. Persistence of PHN for more than 6 months after the healing of skin lesions was observed in 25% of TNF inhibitor-treated patients; comparatively, PHN persistence for 3 months was observed in 2% to 9% of the patients not receiving TNF inhibitor treatment.⁴³ Failla et al observed PHN in 5 of the 20 (25%) patients

treated with TNF inhibitors; thus, PHN is more common in this subset of patients compared to the reference population.³⁸ In contrast, Strangfeld et al reported contradictory results. Their study demonstrated that only 2.4% of herpes zoster patients receiving TNF inhibitor therapy experienced PHN.¹⁹ Another retrospective analysis of 206 herpes zoster patients receiving TNF inhibitors reported only 2 cases of PHN, an unexpectedly low number compared to the incidence reported in other studies.⁴⁴ They assert that although patients treated with TNF inhibitors may present with more severe cases of herpes zoster, complications such as PHN appear to occur less frequently. This phenomenon may be secondary to the role of TNF in mediating neurologic pain.⁴⁴

Management of Herpes Zoster in Patients Receiving Anti-TNF Therapy

Given the complications of this disease, guidelines for antiviral medications have been developed for patients who present with herpes zoster. Primary goals in the treatment of herpes zoster include improvement in outcomes concerning the quality of life of the affected patients, and reduction of the extent, duration, and intensity of cutaneous symptoms including acute pain. Since PHN is the most frequent complication of herpes zoster, reducing its incidence is a major secondary treatment goal.¹

Antiviral therapy is recommended for those aged over 50 years, those with moderate to severe pain, severe rash, face or eye involvement, or other systemic complications, and for all immunocompromised patients.^{1,45,46} Antiviral medications are most effective when initiated within 72 hours of the appearance of rash.⁴⁷ In the absence of risk factors for complications, herpes zoster usually is a self-limiting disease.¹

Oral therapy with either valacyclovir (1 g thrice daily) or famcyclovir (500 mg thrice daily) for 7 days is preferred to oral acyclovir due to increased bioavailability and a more simplified dosing schedule. Intravenous acyclovir (10 mg/kg) every 8 hours for 7 to 14 days (adjusted for renal function) may be administered for more complicated cases such as disseminated and ophthalmic herpes zoster.²²

Guidelines have been developed for the treatment and prevention of herpes zoster in many immunocompromised situations, but limited information has been published to date regarding infections with VZV specifically during treatment with TNF inhibitors or other biologics.

Management of herpes zoster in patients treated with TNF inhibitors may not differ from that of immunocompetent patients, even in severe cases.⁴⁸ The prognosis is usually favorable when the patient is actively treated according to the general guidelines.²¹

In general, the use of TNF inhibitors should be interrupted at the onset of herpes zoster, and can be safely restarted as soon as vesicles have resolved and antiviral therapy is completed.³ However, the decision regarding when to resume

TNF inhibitor therapy is best made on a case-by-case basis, as there is a dearth of evidence in the literature concerning this topic.²² There is 1 small case series of 9 IBD patients with herpes zoster during TNF inhibitor therapy treatment. All patients resumed their anti-TNF therapy after their lesions had completely healed, and only 1 of 9 patients experienced another recurrence 8 months after resuming anti-TNF therapy.²¹

Prevention of Herpes Zoster in Patients Receiving Anti-TNF Therapy

Before the initiation of TNF inhibitor therapy, all patients must be asked about a possible history of recurrent herpes virus infections, varicella, herpes zoster, hepatitis, and HIV infection.

Vaccination remains a potential strategy for reducing the incidence of herpes zoster in the immunocompromised population.² The live zoster vaccine (Zostavax) is a live-attenuated virus vaccine that is 14 times more potent than the varicella vaccine. It is indicated for all individuals older than 60 years who are not vaccinated against varicella with 1 dose of zoster vaccine.⁶ This vaccine has been associated with a 51.3% reduction in the risk of herpes zoster, and prevention of PHN in 66.5% of patients. The efficacy of the vaccine is maintained for at least 6 years.⁴⁹⁻⁵¹

Recently, the new recombinant zoster vaccine (Shingrix) was approved by the US Food and Drug Administration in October 2017 for the prevention of herpes zoster.⁵² This newly developed vaccine utilizes VZV glycoprotein E and a novel adjuvant liposomal delivery system and had shown herpes zoster prevention efficacy of over 97% between 50 and 69 years of age.⁵³ Although there is limited data on the safety of Shingrix in immunosuppressed patients, it may be preferred to Zostavax as it can be safe with concurrent use of TNF inhibitors in psoriasis patients.⁵³

According to recommendations by the Infectious Diseases Society of America, prior to the initiation of immunosuppressive therapy, zoster vaccination could be considered in patients aged 13 to 49 years with chronic immune-mediated or inflammatory disorders, who have a history of varicella or are seropositive despite no history of varicella vaccination.⁶

Meanwhile, there are no known universally accepted guidelines for the prevention of herpes zoster during TNF inhibitor therapy; moreover, limited information is available on the clinical efficacy of zoster vaccine in patients receiving TNF inhibitors. Zhang et al recently showed that in patients exposed to biologics, this vaccine was associated with a lower incidence of herpes zoster (adjusted HR for the vaccine was 0.61) for a median follow-up of 2 years.⁵⁴

With regard to safety of vaccination, the use of live vaccines in patients receiving immunosuppressive drugs can result in disseminated infections. Therefore, it is recommended that live vaccines, including the zoster vaccine,

should be avoided or be given before treatment initiation.⁶ Insufficient evidence is available to determine the safety of the live vaccine, especially in patients receiving TNF inhibitors.

Therefore, it is necessary to delay or interrupt anti-TNF therapy for a certain time period before administering the live vaccine. For patients currently receiving biologics who require live vaccines, recommendations for the administration of the live vaccine should be based on the pharmacokinetic properties of the biologic used. Live vaccines should be given only 6 months and 23 weeks after the last infusion of infliximab and etanercept, respectively.⁵⁵ In addition, the initiation of TNF inhibitor therapy should also be withheld for at least 3 weeks after herpes zoster vaccination, although some experts recommend waiting 4 weeks.⁵⁵

Despite this evidence, several observational studies suggest that the risk of administering live vaccines during treatment with biologics may not be as dangerous as previously believed.^{22,56} In 2012, Zhang et al reported that the live zoster vaccine was not associated with the development of herpes zoster or disseminated infection in immunocompromised patients within the first 42 days of vaccination.⁵⁴ The incidence of herpes zoster in the vaccinated group was also lower than that in the nonvaccinated group after a median follow-up period of 2 years (HR = 0.61; 95% CI = 0.52-0.71).⁵⁴ Another study reported similar results: approximately 6% of the patients who received the live zoster vaccine were concomitantly using anti-TNF therapy, and no patient receiving anti-TNF therapy developed disseminated VZV infection within 30 days of vaccination.⁵⁷

Limitations

This current review is limited by inconsistencies in the reported data. For example, studies report differences in the nature and severity of underlying disease, age-related herpes zoster incidence, inconsistent use of biologics (number and/or duration) as well as combination therapy (ie, methotrexate or corticosteroids), which can increase the risk of herpes zoster incidence. The effects of other drugs used in combination with TNF inhibitors should be included in the factors that may increase the incidence of herpes zoster.

Due to these factors, the efficacy and safety of the herpes zoster vaccine with concurrent treatment with TNF inhibitors may also vary. The only TNF inhibitors included in this study were adalimumab, infliximab, and etanercept due to limited data availability.

Conclusion

Tumor necrosis factor inhibitors have been used as an excellent therapeutic option in a variety of chronic inflammatory conditions, but are not without significant adverse effects. We highlight the incidence, clinical features, management,

and prevention of herpes zoster in patients receiving TNF inhibitors.

In summary, the evidence highlights the importance of herpes zoster prevention in this population, and thus, herpes zoster vaccination is highly recommended before starting infliximab therapy, regardless of the underlying disease. The risk of herpes zoster during adalimumab and etanercept therapy in psoriasis patients remains debatable; however, the zoster vaccine should be considered in inflammatory arthritis or IBD patients with inflammatory arthritis on TNF inhibitor therapy, receiving combination treatment with methotrexate, and those with additional risk factors for herpes zoster. The decision to administer the zoster vaccine prior to starting TNF inhibitor therapy should be made on a case-by-case basis after careful discussion of the risks and benefits between the patients and their physicians.

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