Joint Bone Spine 84 (2017) 21–27

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Review

Herpes zoster: Risk and prevention during immunomodulating therapy

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ARTICLE INFO

Article history:
Accepted 17 February 2016
Available online 28 May 2016

Keywords:
Varicella-zoster virus
Immunomodulators
Biotherapy
Vaccination

ABSTRACT

Herpes zoster can be serious or incapacitating, particularly in patients whose immune system is compromised by a disease or treatment. Immunomodulating drugs can increase the risk of infection. Well-established risk factors include advanced age and glucocorticoid therapy. The data are somewhat conflicting for medications such as methotrexate, tofacitinib, TNFα antagonists (infliximab, adalimumab, etanercept, certolizumab, and golimumab), abatacept, tocilizumab, and rituximab. Nevertheless, the risk of herpes zoster is increased in patients taking biological agents, because of the underlying diseases and/or effects of the drugs. A live attenuated herpes zoster vaccine has been proven effective and safe in immunocompetent individuals. At present, however, it is not recommended for patients with immunodeficiencies, including those taking biological drugs, as no studies have assessed its risk/benefit ratio in this population. This situation may change in the near future, as recent data support the effectiveness and safety of the herpes zoster vaccine in patients who take biotherapies or have other causes of immunodeficiency. Alternative approaches designed to protect these patients from herpes zoster and its complications are also under evaluation. There is a need to define the indications of the herpes zoster vaccine in terms of the target population, timing, modalities, and frequency, according to the underlying chronic systemic disease, age group, varicella-zoster virus status, and exposure to therapeutic agents.

1. Introduction

Herpes zoster is caused by reactivation of the varicella-zoster virus (VZV) [1]. Cellular immunity is the main line of defense against herpes zoster [2]. A decrease in the effectiveness of the cellular immune responses due to age, disease, or treatments may explain the increased risk of herpes zoster in populations exhibiting these risk factors [2]. Asymptomatic episodes of VZV reactivation and exposure to exogenous VZV may help to maintain immunity against the virus [3].

The treatment of systemic inflammatory diseases has been radically transformed by the introduction of immunomodulating drugs such as TNFα antagonists (infliximab, adalimumab, etanercept, certolizumab, and golimumab), abatacept, rituximab, tocilizumab, and tofacitinib. However, these drugs affect the immune system and are associated with an increased risk of infections due to bacteria (e.g., tuberculosis) and viruses. The risk increase occurs not only for primary infections, but also for viral reactivation, for instance of the hepatitis B virus [4] and herpes viruses such as the VZV. Recommendations about vaccinating patients on immunomodulating drugs have therefore been issued, although they are fairly rarely followed in everyday practice [5,6].

Here, we review the latest data on the risk of herpes zoster in adults taking immunomodulating drugs, as well as on available preventive measures. Special emphasis is put on TNFα antagonists, the most extensively studied immunomodulating drug class to date.

2. Risk of herpes zoster during immunomodulating treatment

2.1. Incidence with conventional immunomodulating drugs

Of the many risk factors associated with herpes zoster, the most important are older age [7,8] and immunodeficiency [9,10]. The incidence of herpes zoster increases from about 3/1000 person-years before 30 years of age to 8/1000 person-years after 60 years of age, with variations across studies and populations [7,8]. All types

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http://dx.doi.org/10.1016/j.jbspin.2016.04.001
1297-319X/

Table 1
Immunomodulating drugs and herpes zoster.

Authors	Populations	Treatments	Sample size	Design	Results	95%CI
Wolfe et al., 2006 [17]	RA	TNFαA (I, A, E)	6167	Prospective	I: HR = 1.2	(1.0–1.5)
		DMARD		Multivariate	A: HR = 0.4	(0.2–0.9)
				analysis	E: HR = 0.9	(0.7–1.2)
					MTX: HR = 1.0	(0.8–1.3)
					Leflu: HR = 1.4	(1.1–1.8)
					Aza: HR = 2.0	(1.2–3.3)
					GC: HR = 1.5	(1.2–1.8)
Smitten et al., 2007 [13]	RA	Biologics (I, E, AN)	32	Case-control	aOR = 1.54	(1.04–2.29)
		or DMARD	306		aOR = 1.37	(1.18–1.59)
		or GC	166		aOR = 2.51	(2.05–3.06)
		vs. no GC or DMARDs	877		Reference	
Strangfeld et al., 2009 [19]	RA	TNFαA (I, A, E)	3266	Prospective	aHR = 1.63	(0.97–2.74)
		vs. DMARD	1774		Reference	
McDonald et al., 2009 [22]	RA	TNFαA (I, A, E)	3661	Retrospective	I: HR = 1.32	(0.85–2.03)
					A: HR = 0.53	(0.31–0.91)
					E: HR = 0.62	(0.40–0.95)
		DMARD			MTX: HR = 1.13	(0.75–1.70)
					Leflu: HR = 0.95	(0.58–1.56)
					Aza: HR = 1.06	(0.46–2.40)
		GC			GC: HR = 1.08	(0.69–1.70)
Galloway et al., 2013 [20]	RA	TNFαA (I, A, E)	1,1881	Prospective	aHR = 1.7	(1.1–2.7)
		vs. DMARD	3673		Reference	
Veetil et al., 2013 [14]	RA	TNFαA	137	Retrospective	HR = 1.24	(0.56–2.74)
		DMARD			MTX: HR = 1.34	(0.85–2.10)
		GC			GC: HR = 1.72	(1.03–2.87)
Winthrop et al., 2013 [15]	RA, CIBD, Pso, PsA, SpA	TNFαA (initiation of I, A, E)	33,324	Retrospective	aHR = 1.09	(0.88–1.36)
		vs. DMARD	25,742		Reference	
Che et al., 2014 [21]	RA	TNFαA	Equivalent to 163,077 patient-years	Metaanalysis	Pooled risk ratio = 1.61	(1.16–2.23)
		vs. DMARD			Reference	
Pappas et al., 2015 [7]	RA (CORONA registry)	TNFαA	4321	Retrospective	Reference	
		vs. other biologics (rituximab, abatacept, and tocilizumab)	2170			
					aHR = 0.834	(0.51–1.37)
		vs. DMARD	1505		aHR = 1.359	(0.82–2.25)

95%CI: 95% confidence interval; RA: rheumatoid arthritis; TNFαA: TNFα antagonist; I: infliximab; A: adalimumab; E: etanercept; AN: anakinra; DMARD: synthetic disease-modifying antirheumatic drug; GC: glucocorticoid; CIBD: chronic inflammatory bowel disease; Pso: cutaneous psoriasis; PsA: psoriatic arthritis; SpA: spondyloarthritis; MTX: methotrexate; Leflu: leflunomide; Aza: azathioprine; aOR: adjusted odds ratio; aHR: adjusted hazard ratio.

of immunodeficiency increase the risk, particularly those affecting the cellular immune system [9,10]. The risk of herpes zoster is also elevated in patients with chronic autoimmune or inflammatory diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and chronic inflammatory bowel disease (IBD) [10–14]. In these patients, the risk increase occurs earlier than usual: thus, in populations with RA, the risk at 40–50 years of age is similar to that seen after 60 years of age in the general population, and a risk increase is already apparent at 21–30 years of age in patients with SLE [8]. The excess risk may stem not only from the disease, but also from the drugs used to treat it. No data are available on the incidence of herpes zoster in patients with polymyalgia rheumatica or giant cell arteritis.

Glucocorticoid therapy increases the risk of herpes zoster, 1.5- to 2.5-fold [7,11,13–16]. Although the risk increases with the dose, even low doses are associated with an excess risk [16]. The data on conventional disease-modifying antirheumatic drugs (DMARDs) are more controversial. Some of these drugs may be associated with the occurrence of herpes zoster [13]. Thus, one study showed relative risks of 1.4 with leflunomide, 2.0 with azathioprine, and 4.2 with cyclophosphamide [17]. Others do not seem to have this effect. An example is methotrexate: although several case-reports of herpes zoster during methotrexate therapy have been published, this drug does not seem to be associated with a significant increase in susceptibility to herpes zoster [14,18].

2.2. Incidence during biological therapy

Data on biological drugs are somewhat conflicting (Table 1). Several studies showed an increased risk of herpes zoster in patients taking TNFα antagonists to treat RA [13,19–21]. In a metaanalysis of studies in patients with RA [21], the pooled risk ratio of herpes zoster during TNFα antagonist therapy compared to synthetic DMARD therapy was 1.61 (95%CI, 1.16–2.23). Other investigations, however, produced different findings [7,14,15,17,22,23]. A retrospective cohort study [15] assessed the incidence of herpes zoster in patients with various inflammatory diseases, with special attention to the potential effect of TNFα antagonists. There were 310 cases of herpes zoster among 33,324 patients taking TNFα antagonists. The risk of herpes zoster was not higher with TNFα antagonists than with conventional treatments. In contrast, an excess risk of herpes zoster was demonstrated with other biological drugs such as tofacitinib [24], and this risk was further increased by the concomitant use of conventional DMARDs or glucocorticoids [25]. The risk of herpes zoster may vary across biologics. Among TNFα antagonists, infliximab seems to carry the greatest risk of herpes zoster [19,20,22,26,27]. However, discrepancies also exist among data on this point. Thus, in a retrospective cohort study of 29,129 patients who had recently started a TNFα antagonist, abatacept, rituximab, or tocilizumab, no significant differences were found across these drugs [16] (Table 2).