

Antiviral treatment for shingles and its complications in immunocompetent adults

Description of the topic

Shingles (herpes zoster) is an acute infection caused by the reactivation of the chicken pox virus (varicella zoster). Following a primary infection with varicella zoster, the virus lies dormant in the dorsal root ganglia until it is reactivated and travels along the sensory nerve fibres to cause a vesicular rash.¹ The rash is usually unilateral and most commonly affects the thoracic (chest) nerves, followed by the ophthalmic branch of the trigeminal nerve.^{1,2} Paraesthesia and pain may occur 2–3 days prior to the onset of the rash.² Lesions develop for about 3–5 days, following which the lesions pustulate and scab over within the next 7 days.^{1,3} The rash is associated with pain in 60–90% of immunocompetent adults.³ The pain can be constant or intermittent and is described as stabbing, tender, throbbing, itchy or hot.^{2,3}

While the pain associated with the acute phase of infection tends to resolve with the rash, chronic pain can persist in the dermatome (skin that is innervated via a single nerve) affected by herpes zoster and be debilitating. This is known as postherpetic neuralgia (PHN) and is the most common complication of shingles. In a UK general practice study, PHN developed in over 20% of 60–65 year olds who had had acute shingles and in 34% of those aged 80 years and over.⁴ The second most common complication is ophthalmic zoster affecting 20% of people with shingles and can lead to complications of the eye such as conjunctivitis, scleritis, uveitis and keratitis.^{2,3}

Key points

- Anti-viral drugs – aciclovir, famciclovir and valaciclovir – are all licensed for use in the UK for the treatment of shingles, and should be administered within 72 hours of the onset of the rash.
- It is clinically proven that antiviral therapy is safe and can accelerate rash healing and reduce the intensity and duration of pain in the acute phase of shingles. There is some evidence that antiviral agents can reduce the duration of PHN, with newer agents being modestly more effective.
- Antiviral drugs are effective in reducing the frequency and severity of ophthalmic shingles, and can be initiated beyond the recommended 72-hour time frame.
- Aciclovir is cheaper than famciclovir and valaciclovir as it is available in generic form.

Health technology

Shingles is a self-limiting disease but can be treated with antiviral agents. Aciclovir, famciclovir and valaciclovir are all licensed for use in the UK for the treatment of shingles. These drugs can be given orally (aciclovir can also be administered intravenously) and treatment should be administered within 72 hours of the onset of the rash.⁵ This group of antiviral drugs block virus replication and slow down its spread. Aciclovir (800 mg five times daily for 7–10 days) was the first antiviral developed to treat shingles but has limited oral bioavailability. Famciclovir and valaciclovir were developed to overcome its

limitations and have improved pharmacokinetic profiles.³ They have different regimens: 250 mg three times daily or 750 mg daily for 7 days for famciclovir and 1 g three times daily for 7 days for valaciclovir.

Epidemiology

Shingles can cause considerable morbidity as the pain associated with the illness can be debilitating and reduce quality of life. Shingles is more common among immunocompromised individuals, such as people receiving chemotherapy, people with HIV and people with lymphoma, and can be fatal.¹

About one in five people will get shingles at some point in their lifetime, although the incidence of shingles increases with age.² It is rare in people aged under 50 years occurring in approximately <2/1,000 patients per year, but increases to 5–7/1,000 patients a year in the 50–79 year age group and further to 11/1,000 patients per year in those aged 80 years and older.⁴ The risk of a second episode of shingles is less than 5%.² Based on a general practice population of 1,500 patients, it is anticipated that 3–5 cases of shingles would be diagnosed each year.¹

In the acute phase of shingles, the rash usually heals within 2–4 weeks and there may be some scarring. People with shingles are infectious until the lesions crust over. Varicella-zoster virus can be transmitted to non-immune individuals, resulting in chickenpox (and not shingles). While PHN is usually a self-limiting illness with prevalence decreasing over time, in some cases it can persist for months or even years. Results from a UK general practice survey reported that 2% of people had pain for more than 5 years after an episode of shingles.² The main risk factor of PHN is increasing age (greater than 50 years). Other risk factors include female gender, severe or disseminated rash and severe pain at presentation (visual analogue scale>5).¹

Identifying patients who are most likely to develop PHN and would benefit from antiviral treatment is important.

In the UK, shingles and PHN costs the national health service (NHS) up to £73.8 million each year. It has been estimated that an episode of acute shingle results in NHS costs of approximately £125 and up to £777 for an episode of PHN.⁶

Clinical effectiveness of antiviral treatment

The aim of antiviral treatment for shingles is to reduce acute pain, to accelerate cutaneous healing, to limit the spread and duration of rash in the acute phase, and to prevent PHN and other complications of shingles.

The efficacy of oral antiviral agents has been demonstrated in a number of randomised controlled trials (RCTs). A series of randomised studies of aciclovir compared with placebo showed that aciclovir reduced the duration of virus shedding and new lesion formation, and accelerated rash healing in patients with shingles.³ A systematic review reported that four placebo-controlled trials provided some evidence for the reduction of PHN at 1 – 3 months⁷, but no significant difference in pain between aciclovir and placebo at 6 months.⁴ The studies were too heterogenous for meta-analysis to be performed. Of the newer antiviral agents, famciclovir has been evaluated at two doses (500 mg and 750 mg three times daily for 7 days) in a large placebo-controlled study which showed that neither famciclovir dose showed a reduction in acute pain compared with placebo.³ However, both doses of famciclovir significantly decreased the duration of pain in patients who developed PHN compared with placebo (63 day and 61 days vs 119 days; P=0.02, P=0.01 respectively).^{4,8} However, these doses are higher than those licensed for use in the UK.²

There have been several head-to-head comparisons of aciclovir with the newer antiviral agents and between the newer agents. Evidence from one RCT comparing 1 g valaciclovir given three times daily for 7 or 14 days with standard dose of aciclovir for 7 days showed that all treatment regimens had similar effects on rash healing but both valaciclovir regimens were faster at resolving pain by 1–2 weeks (38 and 44 days vs 51 days). Furthermore, patients treated with valaciclovir demonstrated a lower prevalence of PHN at 6 months compared with those on aciclovir (pooled data 18.6% vs 25.7%; $P=0.02$).^{2,4}

Two further dose-ranging studies compared three doses of famciclovir with aciclovir. The first of these showed that famciclovir 250 mg three times daily and 750 mg once daily for 7 days were as effective as aciclovir in terms of rash healing and the loss of acute pain.^{2,9} Within the second study, reduced duration of PHN was seen with all doses of famciclovir (250 mg, 500 mg and 750 mg three times daily for 7 days; note the latter two doses are higher than those licensed in the UK) given within 48 hours of rash onset compared with acyclovir, but this difference was only significant for the 500 mg famciclovir dose.^{2,10}

Equivalence has been demonstrated in an RCT comparing the two newer antiviral agents. The study found no statistical or clinical differences between famciclovir and valaciclovir with respect to rash healing, and resolution of acute pain and PHN.^{2,3}

Collectively, the findings from these clinical trials provide support for using antiviral therapy to reduce the duration of virus shedding and lesion formation, accelerate rash healing and reduce the intensity and duration of pain in the acute phase of shingles. While there is some evidence that aciclovir reduces the

duration of PHN compared with placebo, more convincing evidence with the newer antiviral agents exists; however, the doses in famciclovir trials exceeded those licensed in the UK. The evidence for antiviral agents in reducing the incidence of PHN is less clear.⁷

The success of antiviral treatment depends on the starting point of therapy. Treatment should be initiated within 72 hours of rash onset while viral replication is still taking place.^{1,11} Delays in diagnosing infection, late presentation to healthcare facilities and difficulties in accessing treatment, for example, over the weekend or during public holidays, may cause delays in patients starting therapy within this time frame.^{3,12}

Ophthalmic shingles

The main goal of treating ophthalmic shingles with antiviral therapy is to prevent potentially severe complications of the eye. There is limited data on the efficacy of oral antiviral therapy in ophthalmic shingles. Two placebo-controlled studies for aciclovir and two RCTs comparing newer agents with aciclovir (dose used in famciclovir trial is not licensed in UK) showed that antiviral drugs are effective in reducing the frequency of both early and persistent complications of the eye and their severity.^{2,3} For complications of the eye, antiviral therapy can be started even beyond the 72-hour window.¹

In addition, guidelines recommend that patients with ophthalmic complications should be referred for specialist ophthalmic management as soon as possible.^{3,11-13}

Who should receive oral antiviral therapy

UK guidelines recommend that oral antiviral drugs at licensed doses should be given in

immunocompetent adults aged over 60 years, those with ophthalmic involvement regardless of age and patients with active zoster affecting the neck, limbs and perineum. It should also be considered in patients who present with severe pain.¹³

Guidelines from US, European and international authors recommend antiviral drugs in immunocompetent adults aged 50 years and over and in adults of any age who present with moderate or severe acute pain or extensive rash, or have ophthalmic involvement, or have severe atopic dermatitis or eczema.¹¹⁻¹³ Opinion is divided on treating adults under the age of 50 years for the prophylaxis of PHN and other complications of shingles.^{2,12}

Safety

The safety profiles of aciclovir, famciclovir and valaciclovir are generally good. The most common adverse effects experienced with these agents are nausea (with occasional vomiting) and headache but trials have reported similar frequencies of these events in both treatment and placebo groups.^{3,12}

Cost effectiveness

Of the three antiviral agents available to treat shingles, only aciclovir is available in generic form and is therefore cheaper than famciclovir and valaciclovir which are still protected by patent.¹²

Two US studies were identified which examined the cost effectiveness of antiviral agents using decision-analysis techniques. The first of these studies compared famciclovir or valaciclovir with no antiviral agent and concluded that treating severely symptomatic shingles within 72 hours of rash onset was cost effective. Treatment of mildly symptomatic patients was likely to be considered

Acknowledgements

NHS Quality Improvement Scotland would like to acknowledge the helpful contribution of the following, who gave advice on the content of this Evidence Note:

- Dr John Nugent, Clinical Director, West Community Health & Care Partnership, NHS Greater Glasgow & Clyde
- Professor Andrew Power, Head of Prescribing Team, Pharmacy & Prescribing Unit – Victoria Infirmary, NHS Greater Glasgow & Clyde
- Dr Roger Hardman, General Practitioner, NHS Greater Glasgow & Clyde

NHS QIS Development Team

- Mrs Emma Riches, Medical Writer
- Ms Alison Winning, Senior Health Information Scientist
- Mr Patrick Maitland-Cullen, Assistant Information Scientist
- Miss Jennifer Graham, Project Officer
- Ms Ailsa Brown, Evidence Note Co-ordinator
- Dr Susan Baxter, Health Services Researcher

cost effective when the risk of PHN is high.¹⁴ The second study estimated the incremental cost effectiveness of antiviral treatment in different age groups and disease severity, and concluded that it was economically justifiable to treat patients of all ages with severely symptomatic acute shingles and patients aged 50–60 years or older with milder shingles when presenting within 72 hours of rash onset.¹⁵ The authors of these studies concluded that if there is no difference in clinical effectiveness among the antiviral drugs, the least expensive drug is the most cost effective.¹⁴ However, these studies were published in 1998 and 2000, and no recent and appropriate studies were identified.

About Evidence Notes

- For further information about the Evidence Note process, see www.nhshealthquality.org
- To propose a topic for an Evidence Note, email evidencenotes@nhshealthquality.org
- References can be accessed via the internet (where the addresses are provided), via the e-library (www.elib.scot.nhs.uk), or by contacting your local library and information service.

Equality and Diversity

NHS QIS is committed to equality and diversity. This document, and the research on which it is based, have been assessed for any likely impact on the six equality groups defined by age, gender, race/ethnicity, religion/faith, disability and sexual orientation. For a summary of the equality and diversity impact assessment, please see <http://www.nhshealthquality.org/nhsqis/files/EQRIA0021>

References

1. Wareham DW and Breuer J. Herpes zoster. *Br Med J*. 2007;334:1211-5.
2. Clinical Knowledge Summaries. Shingles and postherpetic neuralgia [online]. 2005 [cited 2007 Oct 30]; Available from: http://www.cks.library.nhs.uk/shingles_postherpetic_pain/view_whole_guidance
3. Johnson R, Patrick D, editors. Improving the management of varicella, herpes zoster and zoster-associated pain. Recommendations from the IHMF Management Strategies Workshop [online]. 2002 [cited 30 Oct 2007]; Available from: http://www.ihmf.org/library/down_m11.asp
4. Wareham D. Postherpetic neuralgia. *BMJ Clinical Evidence* [online]. 2007 [cited 2007 Oct 30]; Available from: <http://clinicalevidence.bmj.com/ceweb/conditions/ind/0905/0905-get.pdf>
5. British National Formulary 54. Herpes simplex and varicella-zoster infection [online]. 2007 Sept [cited 2007 Oct 30]; Available from: <http://www.bnf.org/bnf/bnf/54/128402.htm>
6. Edmunds WJ, Brisson M and Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. *Vaccine*. 2001;19(23-24):3076-90.
7. Alper BS and Lewis PR. Does the treatment of acute herpes zoster prevent or shorten postherpetic neuralgia? A systematic review of the literature. *J Fam Pract*. 2000;49(3):255-64.
8. Tying S, Barbarash RA, Nahlik JE, Cunningham A, Marley J, Heng M et al. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia. A randomized, double-blind, placebo-controlled trial. Collaborative Famciclovir Herpes Zoster Study Group. *Ann Intern Med*. 1995;123(2):89-96.
9. Shafran SD, Tying SK, Ashton R, Decroix J, Forszpaniak C, Wade A et al. Once, twice, or three times daily famciclovir compared with aciclovir for the oral treatment of herpes zoster in immunocompetent adults: a randomized, multicenter, double-blind clinical trial. *J Clin Virol*. 2004;29(4):248-53.
10. Degreef H and Famciclovir Herpes Zoster Clinical Study Group. Famciclovir, a new oral antiherpes drug: results of the first controlled clinical study demonstrating its efficacy and safety in the treatment of uncomplicated herpes zoster in immunocompetent patients. *Int J Antimicrob Agents*. 1994;4(4):241-46.
11. Gross G, Schöfer H, Wassilew S, Friese K, Timm A, Guthoff R et al. Herpes zoster guideline of the German Dermatology Society (DDG). *J Clin Virol*. 2003;26(3):277-89.
12. Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M et al. Recommendations for the management of herpes zoster. *Clin Infect Dis*. 2007;44(Suppl 1):S1-S26.
13. Johnson R, Mandal B, Bowsher D, Breuer J, Cook S, Griffiths P et al. Guidelines for the management of shingles. Report of a working group of the British Society for the Study of Infection (BSSI). *J Infect*. 1995;30(3):193-200.
14. Smith KJ and Roberts MS. Cost effectiveness of newer antiviral agents for herpes zoster: is the evidence spotty? *J Infect Dis*. 1998;178(Suppl 1):S85-S90.
15. Smith KJ and Roberts MS. Antiviral therapies for herpes zoster infections. Are they economically justifiable? *Pharmacoeconomics*. 2000;18(2):95-104.