Beyond efficacy: new issues for HSV antiviral therapy

Additional therapeutic options for genital herpes have become available in the past year, raising new questions about the optimum management of this widespread infection. While the new prodrugs, valaciclovir and famciclovir, have been shown to be effective as episodic treatments for herpes recurrences,1-7 this issue of *Genitourinary Medicine* presents the first published study of valaciclovir as suppressive therapy for herpes simplex virus (HSV). Patel and colleagues (p 105) demonstrate in a blinded, randomised, controlled trial that valaciclovir 500 mg once daily effectively suppresses recurrence of genital herpes among patients with at least eight recurrences per year. The relative risk of a recurrence was 6-5 fold (95% confidence interval 4-7, 8-9) higher among patients receiving placebo than patients receiving valaciclovir. How are we to evaluate these new therapeutic options for patients with genital herpes and decide what is the best therapy? The answer partly depends on who "we" are and how we define "best" outcome. The interested parties include people with genital herpes, physicians, and, increasingly, healthcare organisations which decide, often on financial grounds, which medications are available. For treating physicians, there are sufficient data on the efficacy and safety of these therapies. Other issues, such as cost, convenience, and quality of life, therefore, may become increasingly important.

Studies with aciclovir, valaciclovir, and famciclovir have shown these drugs are effective in the acute therapy of recurrent episodes of genital herpes.1-5 In addition, aciclovir effectively suppresses recurrences when taken daily, as do valaciclovir and famciclovir.6-13 All three drugs demonstrate superiority compared with placebo. While their effectiveness has not been compared directly, it seems likely that the three drugs will not differ markedly in performance and that all will be effective in preventing most recurrences.

Aciclovir has claims to safety substantiated by 15 years of clinical experience. A small cohort of patients has used it daily for up to 10 years.8-9 While such long term administration is not desirable for most patients, it is encouraging that the drug is so well tolerated. Both valaciclovir and famciclovir need more time before their long term safety is known, but the currently available data are reassuring.

The appearance of a thrombotic microangiopathy in about 3% of immunocompromised patients receiving 8 g a day of valaciclovir for the prevention of cytomegalovirus disease has not been observed in patients receiving lower doses, including 3 g a day for the treatment of varicella zoster.9 Whether the development of this complication is related more to the dose of valaciclovir or to the underlying immunosuppression is impossible to untangle at this time. In any case, such large doses of valaciclovir are unlikely to be used in healthy hosts, as herpes simplex virus and varicella zoster virus respond readily to lower doses.

Beyond safety and efficacy, convenience and cost will become the next factors for evaluating these therapies. Valaciclovir has an advantage over aciclovir and over famciclovir as it is effective when taken once daily, while studies with the latter agents indicate that they must be taken at least twice daily to suppress recurrences adequately.10-12 Despite studies that suggest that patients’ adherence to the therapeutic protocol benefits from once a day dosing,14 it is not clear what happens when a dose is missed from a once daily versus twice daily antiviral regimen. While the patient who receives once daily therapy may be compliant on a higher percentage of days, the patient who receives twice daily therapy may actually take a higher percentage of the prescribed medication. The relation of a missed dose versus a missed day of medication and breakthrough recurrences and the potential for subclinical shedding during that time has not been evaluated. In our study of suppressive aciclovir,15 we found that most of the breakthrough shedding was not related to lack of adherence to the protocol. This would have been an interesting issue to examine in the study of Patel *et al.* Another issue to consider is the cost of the drugs. This depends not only on the dosage used but may also be influenced by purchasing power of large healthcare organisations, which may be able to negotiate significant discounts on purchases. The availability of generic aciclovir may offer another economic alternative.

Which patients should be treated? General agreement exists that "severe" clinical illness caused by genital HSV ought to be treated. This includes patients with clinical first episode infection, recurrent disease with more than six recurrences per year, and less frequent but severe recurrences of HSV which cause morbidity. Antiviral therapy of first episode genital herpes reduces the duration of the episode, prevents formation of new lesions and decreases the frequency of neurological complications.16-18 For many healthy young people primary genital herpes is the most severe illness experienced. The misery of primary genital herpes most probably contributes to the long term psychosocial impact of this illness as well. Unfortunately, even when administered promptly, antiviral therapy does not affect the natural history of the disease.19

For recurrent episodes, antiviral therapy shortens the duration of lesions and symptoms associated with the recurrence. The earlier research with aciclovir suggested marginal benefit from therapy of acute episodes. In the recent trials conducted with valaciclovir and famciclovir, the benefit appears clinically significant, as the duration of the episodes was decreased by about one third.1,2 The improved outcome with the use of these agents when compared with aciclovir trials done a decade ago may reflect a more frequent schedule of patient evaluation in the clinical trial and the use of patient initiated treatment.
regimens rather than a better antiviral performance of the new agents.

Overall, individuals with severe clinical disease represent only a fraction of the HSV infected people and the benefit of antiviral treatment in the majority of infected people has not been evaluated. Generally, recurrent episodes are mild and short lived: most patients rate the discomfort of recurrences as mild or moderate, and only 5% characterise it as severe. However, the psychosocial dysfunction which occurs in people who have acquired genital herpes is considerable and can persist for many years, often increasing in intensity during recurrences.20 22 Fear of rejection, isolation, and discovery is common, as are feelings of depression and self-destructiveness. While many of these feelings wane in intensity as the individual adjusts to living with a chronic sexually transmitted and contagious illness, for some these feelings persist and interfere seriously with normal social and sexual function.

Aside from research studies which focus on the biologic benefits of antiviral therapy, little information is available about other potential gains. What is the effect of suppressive therapy on the quality of life? Does antiviral therapy aid psychosocial adjustment? Does it reduce the risk of transmission to susceptible partners? Since most patients experience only mild to moderate discomfort with recurrences, their interest in suppressive therapy probably reflects more than desire to avoid the troublesome ulcerations. One study suggests that suppressive aciclovir has a favourable effect on the psychosocial morbidity in people with frequent recurrences;23 more data on the psychotherapeutic effect of antiviral agents are needed. Quality of life has become increasingly popular to measure in trials of therapies for chronic illness,24 and instruments for measuring quality of life have been developed for patients with herpes.25 Their use in the assessment of antiviral drugs should provide helpful guidelines on the benefit of therapy.

Economics may also have an important bearing on therapeutic choices in the real world. For example, the expense of daily antiviral therapy may adversely affect the quality of life, a factor not evaluated in clinical trials, as the study medications are provided free of charge. In our clinic, the high cost of suppressive therapy is the most common reason for discontinuation and among the most frequent reasons that patients desire to participate in research protocols of suppressive therapies. Thus, for many patients, the choice of antivirals may depend on their financial situation: patients for whom the expense is not an issue may prefer the once daily dosing, even if the cost is higher, while patients with limited financial resources may choose a less convenient, but more affordable option.

The potential of antiviral therapy to interrupt transmission also has not been evaluated. Aciclovir has been shown to decrease subclinical shedding;11 studies with valaciclovir and famciclovir are in progress. However, as some shedding of HSV in the genital tract persists during therapy with aciclovir,15 16 the efficacy of antivirals in reducing sexual transmission of HSV remains uncertain. Of note, avoiding HSV transmission to sexual partners is the greatest concern of patients with genital herpes and among the most common reasons for taking suppressive therapy, despite lack of data on its effectiveness for that purpose. Studies which address this issue may not only respond to the desire of patients to protect their partners but may also benefit the community.

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