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Valacyclovir for the Management of Herpes Viral Infections

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ABSTRACT

The Herpesviridae family (Types 1-8) continues to inflict considerable morbidity and social stigma upon humanity. Once infected with the herpes viruses, especially Types 1-3, they establish permanent residence within our nervous system and reactivate during periods of stress, trauma, and/or other precipitating factors. To date, there is no cure for herpes viral infections but antivirals can attenuate the symptoms and duration of episodic outbreaks. Prophylactic therapy can suppress recurrences. The first antiviral with selective activity against virus-infected cells is considered to be acyclovir. Our article will highlight the clinical indications of the current generation, valacyclovir, which is a prodrug of acyclovir. We consider valacyclovir as a second-generation antiviral, having taken into account the initial selectivity and safety profile of its progenitor, acyclovir.

Keywords: herpes virus, antiviral, herpes simplex, varicella-zoster

The hallmark of the herpes viruses is their ability to establish permanent residency within the neuronal ganglia of our nervous system and to reactivate during times of stress, trauma, and other precipitating factors. The herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), and varicella-zoster virus (VZV) can be associated with painful, blistering outbreaks that, although they are self-limiting, have been associated with considerable morbidity.

Antiviral medications are the standard of practice in the management of herpes viral infections. Orally administered antivirals, such as valacyclovir (Valtrex[®], GlaxoSmithKline) are prescribed to attenuate the signs and symptoms, reduce the duration of outbreak, and hasten lesion resolution. Our article will focus on the pharmacologic mechanism and diverse clinical indications of one of the second generation antivirals, valacyclovir. The development of the second generation antivirals has been tailored towards enhancing the oral bioavailability and intracellular pharmacokinetics. Valacyclovir provides an excellent safe and effective alternative to its more traditionally prescribed parent compound, acyclovir.

Mechanism of Action

Acyclovir was the first antiviral drug developed for systemic use that exhibited activity preferentially against herpes virus-infected cells. It is a 2'-deoxyguanosine analogue and requires activation by the viral-encoded thymidine kinase followed by cellular kinases. The final product, acyclovir triphosphate, irreversibly inhibits viral DNA polymerase via

Company Name	GlaxoSmithKline
Compound	Valacyclovir
Structure	
Description	Oral prodrug of acyclovir
Antiviral Spectrum	Herpes simplex virus-1 (HSV-1) Herpes simplex virus-2 (HSV-2) Varicella zoster virus (VZV)

Table 1: Chemical description of valacyclovir.

competition with deoxyguanosine triphosphate, preventing further chain elongation. Acyclovir triphosphate's meager production in non-infected cells and its reduced affinity for cellular DNA polymerase limits its potential side-effects. However, acyclovir has poor oral bioavailability and requires either higher dosing or intravenous administration for severe manifestations of herpes infections (i.e., neonatal herpes, herpes encephalitis).

Valacyclovir provides a high bioavailability of acyclovir, 3- to 5-fold higher than that obtained with oral acyclovir, and it is equivalent to plasma levels achieved with doses of intravenous acyclovir (see Table 1).¹ An L-valine ester of acyclovir, valacyclovir is rapidly metabolized into valine and acyclovir by the enzyme valacyclovir hydrolase in the gastrointestinal

tract and liver. Being a prodrug, valacyclovir does not have any antiviral activity until it is biotransformed into acyclovir. The drug may be administered without regard to meals.

Clinical Indications

The antiviral spectrum of valacyclovir encompasses HSV-1, HSV-2, VZV. The predominant clinical indications are orofacial herpes, genital herpes, herpes zoster and to a lesser degree, cytomegalovirus prophylaxis for transplant patients (Table 2). An alternative antiviral for these clinical indications is another second-generation antiviral, famciclovir (Famvir[®], Novartis), the prodrug of penciclovir. These antivirals have limitations as they provide no cure for infections, but instead alter the clinical course of the disease.

Valacyclovir is utilized for the management of orofacial herpes. HSV-1 is primarily associated with this condition. A short course of high dose valacyclovir at 2,000mg twice daily for 1 day is the recommended dose for initial treatment of orofacial herpes, usually commenced during the prodromal phase.² Another study demonstrated that valacyclovir 500mg, po, b.i.d. for 10-14 days is an effective prophylactic strategy against orofacial herpes recurrence starting 1 day prior to laser cutaneous resurfacing.³ Smaller placebo-controlled trials have demonstrated the benefit of valacyclovir 500mg once daily for 4 months as a well-tolerated and effective therapy for the suppression of recurrent herpes labialis.⁴ The higher bioavailability of valacyclovir enables less frequent administration compared to acyclovir.

HSV-2 is accountable for the majority of genital herpes, although HSV-1 is playing an increasing role in the epidemic. Treatment of genital herpes is categorized into primary, episodic, and suppressive regimens. Valacyclovir is approved by the US FDA at 1,000mg, po, two times daily for 10 days for initial onset of genital herpes and at a 3-day, 500mg,

Orofacial Herpes (HSV-1)	Initial therapy: 2,000mg, po, b.i.d. for 1 day Prophylaxis after laser resurfacing: 500mg, po, b.i.d. for 10-14 days
Genital Herpes (HSV-2 or HSV-1)	Initial therapy: 1,000mg, po, b.i.d. for 10 days Episodic therapy: 500mg, po, b.i.d. for 3 days Suppressive therapy (recurrence dependent): <ul style="list-style-type: none"> • 500mg, po, qd for <10 recurrences • 1,000mg, po, qd for ≥10 recurrences HSV infections for HIV-positive: 1,000mg, po, qd Suppressive dosing for primary episode: ongoing trial – 1,000mg, po, qd
Herpes Zoster/ Post-Herpetic Neuralgia	Immunocompetent: 1,000 mg, po, t.i.d. for 7 days Immunocompromised: ongoing trial – 2,000mg, po, t.i.d. for 7 days
Cytomegalovirus	Prophylaxis: renal transplant patients – 2,000mg, po, q.i.d. for 90 days

Table 2: Clinical indications and dosing for valacyclovir

twice-daily course for episodic management of recurrent herpes.⁵ Suppressive therapy is preferred when recurrences are frequent, severe, and/or emotionally disturbing. An open-label study demonstrated the preference of suppressive therapy with valacyclovir as once-daily therapy over the episodic dose of twice-daily therapy with lower recurrence rates and higher satisfaction levels noted in the suppressive cohort.⁶ The treatment stratification of suppressive therapy is based on the annual number of recurrences.⁷ For patients with <10 annual recurrences, 500mg of daily valacyclovir is recommended. For patients with ≥10 recurrences, 1,000mg valacyclovir daily, 250mg valacyclovir twice daily, or 400mg acyclovir twice daily were noted to be beneficial according to a subgroup analysis for different dosages. The once daily dosing provides a more patient-friendly approach, enabling greater compliance with antiviral therapy.⁷ For HIV positive patients, valacyclovir 500mg twice daily or 1,000mg once daily is considered effective.⁸ The suppressive strategy of valacyclovir therapy is being explored for primary episodes of genital herpes. This study is being conducted by Dr. Beutner in Davis. The treatment strategy will evaluate whether suppressive dosing can reduce the frequency and duration of recurrences as initial management for primary genital herpes.

Genital herpes transmission reduction is a recent supplemental indication for valacyclovir. Corey, et al. demonstrated the significant reduction of HSV-2 transmission among heterosexual, discordant couples with once-daily, 500mg valacyclovir.⁹ The study revealed a 50% decrease in HSV-2 acquisition among susceptible partners and a more dramatic 75% symptomatic reduction of HSV-2 among susceptible partners when the infected partner received once-daily valacyclovir for 8 months. When combined with safe sexual practices (i.e., condom use), valacyclovir has been shown to reduce the transmission of genital herpes. The same study noted a reduction in asymptomatic viral shedding as an additional benefit. Most cases of transmission occur during periods of asymptomatic viral shedding.

Valacyclovir is indicated for the management of herpes zoster. Beutner, et al. demonstrated the benefit of valacyclovir 1,000mg 3x daily for 7 days in reducing the duration and proportion of postherpetic neuralgia at 6 months for patients >50 years old in comparison to acyclovir.¹⁰ As well, no additional benefit was noted beyond 7 days of valacyclovir therapy when compared to a 14 day regime. Tyring, et al. conducted a comparison trial of valacyclovir vs. famciclovir, which did not reveal any significant differences between either antiviral in the treatment of herpes zoster.¹¹ The main advantage of valacyclovir would be cost-effectiveness which takes into consideration the cost of patient hospital stay. Although acyclovir is cheaper, the intravenous route is offset by the costs of inpatient hospitalization. Combination strategies for the management of herpes zoster are also being considered. When incorporating an anticonvulsant, such as gabapentin, with an antiviral, such as valacyclovir, patients

exhibited pain reduction in an open-label, pilot trial.¹² Immunocompromised patients, such as HIV and cancer patients, can suffer from more severe manifestations of herpes zoster than immunocompetent patients. There are no current published studies documenting the benefit of valacyclovir for herpes zoster among the immunocompromised. A higher dosing regimen of valacyclovir for acute herpes zoster may provide a convenient, efficacious, cost-effective, and practical alternative to intravenous acyclovir administration for immunocompromised patients. Dr. Tyring is evaluating a higher dose of valacyclovir at 2,000mg, po, 3x daily vs. 1,000mg, po, 3x daily for 7 days as management of acute herpes zoster in immunocompromised patients. The benefit of the higher dosing valacyclovir will be determined after completion of the randomized, double-blinded study. Valacyclovir provides an effective antiviral in the treatment of herpes zoster and further trials of various dosing regimens of the antiviral pertaining to different clinical manifestations of herpes zoster are ongoing.

Cytomegalovirus (CMV) is a major pathogen resulting in considerable morbidity and mortality subsequent to solid organ and bone marrow transplantation. Antiviral prophylaxis offers an effective strategy compared to the wait and treat approach. Prophylactic therapy with valacyclovir 2,000mg, 4x daily for 90 days immediately after renal transplantation reduced the incidence of CMV disease, as well as delaying its onset.¹³ A separate comparison trial of oral valacyclovir vs. oral ganciclovir demonstrated similar levels of safety and efficacy in the prophylaxis of CMV disease after renal transplantation.¹⁴ Valacyclovir is also utilized as preventive therapy for CMV for cardiac and bone marrow transplant recipients.

Conclusion

The role of valacyclovir in the management of herpes viral infections has been illustrated and is being explored for new clinical scenarios. Valacyclovir provides a unique mechanism of enhancing the oral bioavailability of the parent compound, acyclovir, while maintaining the same safety level profile. The simpler dosing schedule allows patients more convenient dosing regimens with less interruption of their activities of daily living. Current trials of valacyclovir for herpes infections among the immunocompromised as well as new dosing regimens for previously established therapeutic indications are ongoing and will serve to enhance our knowledge of the various clinical indications of valacyclovir.

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Clinical Use of RESTYLANE®

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ABSTRACT

There is no ideal filler, nor will there be a single product that can satisfy all requirements. However, RESTYLANE®, a non-animal, stabilized hyaluronic acid (NASHA, Mediscs), is a very versatile augmenting agent. It has been in clinical use for 8 years and experience has shown it to be close to the ideal filler in many respects. This review will outline the background to the use of RESTYLANE®, and will focus on the clinical use of this material.

Key Words: filler, hyaluronic acid, NASHA

The pace of development of filler substances in the last few years has been phenomenal. Consider that for more than 20 years there was only one US FDA approved cutaneous filler device, bovine collagen (Zyderm®/Zyplast®, Inamed Aesthetics). Bovine collagen has several distinct disadvantages. Two skin tests are necessary, producing a minimum 4- to 6-week treatment delay between the initial consultation and the first treatment. Results are short lived, and the thickest collagen, Zyplast®, lasts only 2-4 months. Beading is relatively common because the product becomes firm and nonmalleable soon after injection.

In February 2003, human collagen (Cosmoderm™/Cosmoplast™, Inamed Aesthetics) was approved by the US FDA. In December 2003, the US FDA approved RESTYLANE®, a cross linked nonanimal source hyaluronic acid. Two other forms of cross-linked hyaluronic acid, Hylaform® and Hylaform® Plus (Inamed Aesthetics) were approved by the US FDA in the summer and fall of 2004, respectively. RESTYLANE® is made by *Streptococci* and Hylaform® is derived from chickens' combs. They also differ in the amount and degree of cross-linking, which affects, among other things, duration of effect. Many more fillers are under development, and some are pending US FDA approval.

Considering the complexity of the areas/conditions being treated, as well as the aims and desires of the individual being treated, there is no ideal filler. Furthermore, no single product will be able to satisfy all requirements. However, a product would be useful in the majority of clinical situations with the following properties:

- non-permanent but long-lasting
- have minimal side-effects

- not require allergy testing
- be easy to use/inject
- be cost-effective both to the physician and patient.

RESTYLANE®, a non-animal, stabilized hyaluronic acid (NASHA) is not ideal, but is far closer to this set of criteria than previous fillers.

RESTYLANE® has been available in Europe since 1996, and in Canada since 1998. It is used in more than 60 countries to correct a variety of wrinkles, lines, and contour defects and to enhance the lips. It was approved in the US in December 2003, for use in mid-to-deep dermal implantation for the correction of moderate-to-severe facial wrinkles and folds, such as the nasolabial folds.

Benefits of RESTYLANE® include:

- having a very low allergic potential so that skin tests are unnecessary
- having a very natural look and feel
- lasting significantly longer than any of the collagens
- being moldable and very easy to work with.

Disadvantages include temporary redness and swelling at the injection site, which is most clinically significant when the lips are injected and most often resolves within 3-4 days. Allergic reactions are rare. Most of those reported occurred prior to 2000 when the level of contaminants in the product were dramatically reduced.¹

The best data on RESTYLANE® comes from a study of 138 subjects that led to US FDA approval.² This was a bilateral paired comparison study of the efficacy and safety of

Adverse Effects	RESTYLANE (%)	Collagen (%)
Swelling	87.0	73.9
Tenderness	77.5	64.5
Pain	57.2	42.0
Bruising	52.2	48.6

Table 1: Adverse events in the Resylane®/Zyplast® study²

RESTYLANE® vs. Zyplast® use in the nasolabial folds. The products were injected at baseline, followed by touch-ups as necessary to achieve “optimal cosmetic improvement”. Judging subjects’ folds using a 5-point scale (none, mild, moderate, severe, extreme), both products achieved a 1.5 point improvement. At 6 months, the RESTYLANE® injected side still had a 1 point improvement, whereas the Zyplast® injected side had a 1/3 point improvement. At 6 months after injection RESTYLANE® was considered to be superior in 62% of patients vs. 8% of patients for Zyplast®.

There were more adverse events in the Zyplast®-treated side, but these were mainly minor lumpiness or material showing through the skin. Whereas on the RESTYLANE®-treated side there was more swelling and tenderness (see Table 1).

Other Forms of NASHA

The cross-linked structure of hyaluronic acid forms a gel with limitless molecular weight. This is then passed through screens with varying pore sizes to form the injectables with differing particle sizes. This difference between particle size and molecular weight is an important concept in the field of hyaluronic acid-based materials. Resulting from this, each form of cross-linked hyaluronic acid can be packaged as a number of different injectables. For example, NASHA is packaged as RESTYLANE® Fine Lines (or RESTYLANE® Touch), RESTYLANE® Perlane®, and RESTYLANE® SubQ. Each of these products will be applicable in an appropriate clinical setting. Large studies done with hyaluronic acid show no difference in duration.^{2,3}

Clinical Use

RESTYLANE® is used on the face in a variety of places and for a variety of indications, so for the sake of clarity we shall discuss the uses in different categories, recognizing that, at times, this distinction can be artificial. RESTYLANE® is a very flexible product that can be used for most of the NASHA indications but we shall indicate where we use the different forms of NASHA by preference. Care is always taken to ensure that the product is not injected into a vessel especially when injecting the periocular area.

Fine Lines

Good examples of areas where fine lines are treated would be the glabella, the cheeks, and the perioral area. In these areas we inject RESTYLANE® in the mid-dermis or higher using a serial puncture technique. One should always feel the resistance of the dermis as one is injecting. The glabella and the perioral areas are usually treated in conjunction with BOTOX® (botulinum toxin-A, Allergan) therapy. It is not unusual to have to use RESTYLANE® only once in the glabella if good BOTOX® therapy is maintained afterward. With regard to the fine perioral lines, it is of vital importance NOT to simply inject the lines since this will lift the surrounding skin, reversing the youthful “ski-jump” projection of the lips. We prefer to enhance the vermilion border and perhaps the lips themselves and to only inject the fine radial rhytids very gently. RESTYLANE® Touch is designed for this kind of fine work.

Nasolabial Folds

We frequently use a threading technique along the nasolabial fold, concentrating on the upper Y-shaped area below the nares and lateral to the ala. Deepening of this area is related to age-induced loss of fat so correction will produce a more youthful appearance. Because there is less movement in this area close to the nose, correction persists well. The further down the nasolabial fold one is correcting, toward the smile lines beside the oral commissure, the shorter the duration of the correction. In addition, the smile lines are produced by the expression of a positive emotion and so correction of this area may be less of a priority. Discussion of this differential treatment of the nasolabial folds with the subject prior to treatment is very important. Injection is in the mid-to-deep dermis. Where it is available, RESTYLANE® Perlane is often used for nasolabial fold correction.

Lips

The lips are one of the most important areas for the use of RESTYLANE® and deserve separate discussion. The aim of lip injection is, in younger individuals, to enhance the size and shape of the lips. In older individuals the aim is more one of correction: to get the lips back to where they were rather than to increase their size. For many patients, the aim is a combination of the two. Injecting lips is more likely to produce adverse events than any other area. In particular, short-term swelling is common and bruising is also seen frequently if good technique is not used. In order to limit this effect, the application of ice or ice packs for 5-20 minutes after injection is favored by some.

Though there is nothing in the literature to support its use at this time, some experienced clinicians provide patients with prednisone 30mg to be taken the morning of the procedure and again the next morning; or 30mg to be taken at bedtime on the day of injection if their lips are swollen, and 30mg to take the following morning if their lips are swollen. Using this technique, minimizes swelling which allows the treated

individual to continue with their business and social life rather than having to hide for a day or two. Lip injection is quite uncomfortable. Many use infraorbital and mental nerve blocks to limit discomfort while others prefer distraction techniques such as vibration analgesia.

To limit bruising the needle should be inserted gently through the lip mucosa close to the vermilion and gentle pressure exerted on the plunger. The needle tip can then be advanced using RESTYLANE® to dissect ahead of the tip, and moving blood vessels out of the way (the “push-ahead” technique). It should be possible to reduce the bruising rate to well below 10% using this technique as well as to avoid the use of NSAIDs, etc.

We use a threading technique on the lips. The needle tip is inserted either just mucosal to the vermilion for vermilion enhancement, or 2-3mm on the mucosa for lip enhancement. Gentle pressure on the plunger should produce flow of the RESTYLANE® across the lip in the chosen plane ahead of the needle tip. It is essential to continue the injection into the area of the commissure, and above and below the commissure. RESTYLANE® is our NASHA of choice for lip enhancement.

Contouring

Because of the persistence of NASHA, especially in non-mobile areas, correction of volume loss or enhancement of volume is an increasingly important indication for the use of RESTYLANE®, as well as Perlane® and RESTYLANE® SubQ. Some of the areas where it is used are:

- the temporal eyebrow area to produce a lateral eyebrow lift
- the nasojugal fold to soften the hollows under the eyes (inject just above the periosteum)
- the zygomatic area to enhance the cheekbone
- the infraorbital hollowing to correct age-related fat loss
- the sides of the chin to correct fat loss and to soften the jowls
- the tip of the chin to augment the mentum.

RESTYLANE® is injected deep into these areas with no attempt at dermal injection. We will frequently use a 30 gauge 1" needle, or an even longer needle in order to fan the material deep in the subcutis and then massage aggressively in order to avoid lumpiness. Bruising is a risk when injecting at this level because of the larger vessels so using the “push ahead” technique described under Lips described above will be helpful.

Conclusion

NASHA fillers are very effective. RESTYLANE® lasts twice as long as collagen, no allergy testing is required, and it has an excellent safety profile. Results, however, are highly technique-dependent. The treating physicians must select the subjects and the type of wrinkle or crease carefully, with experience they can become highly skilled in the use of this filler.

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Reviewers for 2004

During 2004, the reviewers noted below gave generously of their time and talents and completed manuscript reviews for the Skin Therapy Letter. On behalf of the Editorial Advisory Board and our readership, we thank them for their efforts.

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
<i>Immunomodulatory Agent</i>	Alefacept <i>AMEVIVE</i> [®] Biogen Idec	TPP Canada authorized the sale of this biologic therapy in October 2004, for the treatment of patients with moderate-to-severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.
<i>Antiacne Agent</i>	Dapsone Gel 5% <i>Aczone</i> [®] Atrix Laboratories	The US FDA accepted an NDA in September 2004, for this gel for the treatment of acne vulgaris. It was formerly called Atrisone.
<i>Anorectal Preparations</i>	Nitroglycerin Ointment <i>Cellegesic</i> [®] Cellegy Pharmaceuticals	The US FDA accepted for review in September 2004, an NDA for this ointment for the treatment of pain associated with anal fissures.
<i>Antibacterial Agent</i>	Cefdinir Oral Suspension <i>Omnicef</i> [®] Abbott Laboratories	The US FDA approved a supplemental NDA in September 2004, for a new 250mg/5ml dosing option of this antibiotic for use in pediatric patients 6 months to 12 years of age. The more concentrated formulation allows parents to administer fewer teaspoons per dose of the antibiotic to their children.
<i>Medical Device</i>	Ultrasonic Skin Permeation Device <i>SonoPrep</i> [®] Sontra Medical	The US FDA gave marketing clearance in August 2004, to this ultrasonic skin permeation device and procedure tray for use with topical lidocaine. This device applies low frequency ultrasound to a patient's skin for approximately 15 seconds to create imperceptible, reversible micro-channels through the stratum corneum making the skin permeable so that the onset of action for transdermal drugs is accelerated.
<i>Antipsoriatic Agent</i>	Tazarotene Capsules Allergan	The US FDA issued a nonapprovable letter in September 2004, for this oral treatment for the treatment of psoriasis. They listed three nonapprovability issues: 1) The need for the development of an acceptable risk management program (which Allergan is in the process of developing); 2) The need for completion of a noninferiority study in severe psoriasis; 3) Satisfaction of a US FDA deficiency letter regarding the manufacture of the oral tazarotene capsules. Allergan is working with the US FDA to resolve these issues.
Drug News		
<i>Drug Warning</i>	The US FDA and Abbott Pharmaceuticals notified healthcare professionals in November 2004, of revisions to the WARNINGS section of the prescribing information, indicated for HUMIRA [®] (adalimumab) which is indicated for the treatment of rheumatoid arthritis. Serious infections have been reported with the combined use of HUMIRA [®] and anakinra (Kineret [®] , Amgen), including hypersensitivity reactions, such as anaphalaxis, and hematologic events such as pancytopenia and aplastic anemia.	
<i>US FDA Regulatory Changes</i>	The US FDA announced in November 2004, that the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 made significant changes to the generic drugs approval process designed to provide more certainty to the generic drug approval process and help get generic drugs to the market more quickly. A guidance of industry entitled "Listed Drugs, 30-Month Stays, and Approval of ANDAs and 505(b)(2) Applications Under Hatch-Waxman, as Amended by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003: Questions and Answers" is being made available at http://www.fds.gov/cder/guidance/6174dft.pdf .	

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