REVIEW ARTICLE

Recent New Drug Approvals. Part 1: Drugs with Pediatric Indications

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This two-part review provides information about drugs that have been recently approved by the Food and Drug Administration and focuses on drugs approved with pediatric indications or approved in adults with active pediatric studies. Information was obtained from the product labeling and selected published studies. Part 1 reviews recently approved drugs with labeled pediatric indications, and Part 2 will review recent drug approvals in adults that have potential use in pediatrics and have active studies.

INDEX TERMS drug approval, drug industry, Food and Drug Administration, pediatric

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INTRODUCTION

This article reviews recently approved drugs that have pediatric labeling information. The significant increase in the number of drugs that have pediatric labeling is the result of two companion laws, the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). The BPCA encourages and provides an incentive for completing important pediatric studies, and the PREA requires drug manufacturers to complete studies in children for the same adult indications when it is expected the drugs will be used in a substantial number of children. Together these two laws have been invaluable in adding information to the drug label on the safe and effective use of more than 400 drugs in children.

CENTRUROIDES (SCORPION) IMMUNE F(ab')₂ (EQUINE) (ANASCORP); APPROVAL AUGUST 4, 2011

The sting of a scorpion is associated with local pain and swelling but rarely requires medical attention. The Arizona bark scorpion (*Centruroides sculpturatus*) sting however can warrant medical treatment (Figure 1). *Centruroides* can be found primarily in the southwest United States and

Figure 1. The Arizona bark scorpion.

Mexico. Scorpion venom is a heterogeneous mixture of toxins that can function as neurotoxins, cardiotoxins, nephrotoxins, and hemolytic toxins. Signs and symptoms can vary from mild local manifestations to severe life-threatening conditions including cardiogenic failure, respiratory failure, and neurological failure. Antivenom therapy is indicated for severe systemic manifestations.¹

Indication(s)

Centruroides (scorpion) immune F(ab')₂ (equine) antivenom (Anascorp; Accredo Health Group, Inc., Memphis, TN) is indicated for the treatment of patients with clinically important

signs of scorpion envenomation, including loss of muscle control, abnormal eye movements, slurred speech, respiratory distress, excessive salivation, frothing at the mouth, and vomiting.² Fortunately, death from scorpion sting is rare in the United States, with only 4 deaths reported in 11 years, but is a major health problem in tropical countries.³

The efficacy of this agent was established from a prospective, randomized, double-blinded, placebo-controlled study of 15 subjects, four open label studies, and one retrospective study in both the United States and Mexico evaluating a total of 1534 patients ranging in age from less than 1 month to 90 years old.⁴ The majority of patients (78%) were children. Treatment success was assessed by resolution of clinically important signs of scorpion envenomation within 4 hours of starting the infusion. In the prospective double-blinded study, symptom resolution was 100% for the scorpion antivenom and 14.3% in patients who received placebo.⁵ In uncontrolled studies, 95% to 100% of patients treated with the scorpion antivenom had symptom resolution compared to 3.1% in patients who received no treatment.⁴

Clinical Pharmacology

The antivenom is composed of venom-specific F(ab')₂ fragments of immunoglobulin G. The antivenom binds and neutralizes venom toxins, facilitating redistribution away from target tissues and elimination from the body.

The pharmacokinetics of scorpion antivenom was studied in 8 healthy volunteers given an intravenous dose.⁶ Elimination half-life was between 6 and 7 days, and volume of distribution was relatively small at 13.6 L. There are no studies to date assessing potential drug interactions with *Centruroides* antivenom.

Dosage and Administration

Centruroides antivenom is a sterile, lyophilized, polyvalent preparation of equine immune globulin F(ab')₂ fragments prepared from hyper-immune horse plasma.⁴ Each vial contains not more than 120 mg of protein and not less than 150 median lethal dose (LD₅₀) (mouse) neutralizing units. The initial dose is three vials. Each vial is diluted with 5 mL of normal saline. The combined contents of the three vials are further diluted to a total volume of 50 mL with normal saline. The solution is inspected for particulate

matter and discoloration. The solution is infused intravenously over 10 minutes, and the patient is monitored for an additional 60 minutes to determine if signs of envenomation have resolved. If symptoms do not resolve, additional doses can be given, one vial at a time every 60 minutes, following the same dilution, administration, and monitoring procedures. There is no recommendation for the maximum number of vials a patient can receive.

Comments

The most common observed adverse effects occurring in 1% to 5% of patients were vomiting, pyrexia, rash, nausea, pruritus, headache, rhinorrhea, myalgia, fatigue, cough, diarrhea, and lethargy. Severe hypersensitivity reactions, including anaphylaxis, may occur. Delayed allergic reactions (serum sickness) were observed in 0.5% of patients treated in clinical trials. Severe hypersensitivity reaction may occur, and patients with known allergies to horse proteins are at increased risk for an anaphylactic reaction. Close patient monitoring during the infusion is recommended, with immediate availability of intravenous drug therapy to treat hypersensitivity reactions including epinephrine, corticosteroids, and diphenhydramine.

CLOBAZAM (ONFI); APPROVAL OCTOBER 24, 2011

Lennox-Gastaut syndrome (LGS) is a severe type of childhood epilepsy that most commonly presents between 3 and 10 years of age. It is associated with developmental delay and multiple seizure types, including drop seizures, and is refractory to most antiepileptic medications. LGS has a poor prognosis, and it is estimated that only 10% of patients experience full remission of seizures with current available therapies.⁷ Clobazam (Onfi, Lundbeck Inc., Deerfield, IL) has demonstrated efficacy as an adjunctive therapy for LGS.^{7,8}

Indication(s)

Clobazam is approved for adjunctive treatment of seizures associated with LGS in patients 2 years of age and older.⁹ Efficacy was established in a phase III, randomized, placebo-controlled trial in patients 2 to 60 years old. Almost 80% of patients enrolled after a protocol amend-

ment completed the study (n=125). The primary outcome measure was percentage decrease in average weekly drop seizure rates. These mean rates decreased 12.1% for placebo versus 41.2%, 49.4%, and 68.3% for clobazam, in dosing groups of 0.25-, 0.5-, and 1.0 mg/kg/day.⁶

Clinical Pharmacology

Clobazam is a 1,5-benzodiazepine (Figure 2) and was initially developed to decrease adverse effects associated with 1,4-benzodiazepines (diazepam, lorazepam, clonazepam, and other forms) while still maintaining efficacy. The mechanism of action is not fully understood, but it is thought to bind to the $\alpha 1$ subunit of the γ -aminobutyric acid (GABA) receptor, causing an increase in GABA-mediated inhibitory effects.⁷

Clobazam is rapidly absorbed and distributed throughout the body after oral administration. Peak plasma concentration and area under the curve (AUC) of clobazam are dose-proportional with linear pharmacokinetics. *N*-desmethyloclobazam is an active metabolite of clobazam and has approximately 1/5 of the parent drug activity. Both clobazam and its active metabolite are extensively metabolized by the liver through CYP3A4 and CYP2C9, respectively. The estimated half-lives of clobazam and *N*-desmethyloclobazam are 36 to 42 hours and 71 to 82 hours, respectively.⁹

Clobazam is a weak CYP3A4 inducer. Because some oral contraceptives are metabolized by CYP3A4, their effectiveness may be reduced, and additional forms of contraception are recommended while taking clobazam. Medications that inhibit CYP2C19 may increase serum concentrations of *N*-desmethyloclobazam, so dosage adjustment may be necessary. Clobazam is a central nervous system (CNS) depressant, so this drug should be used with caution with concomitant administration of other CNS depressants. Also, alcohol increases exposure of clobazam by approximately 50%, so these effects may be potentiated even further.⁹

Dosage and Administration

Clobazam is available as 5-, 10-, and 20-mg tablets. In patients weighing ≤ 30 kg, 5 mg of clobazam daily should be initiated and titrated as tolerated up to 20 mg daily. In patients >30 kg, the starting dose is 10 mg daily and can be titrated up to 40 mg daily. Due to the long half-life

Figure 2. Chemical structure of clobazam.

of clobazam and its active metabolite, dose escalation should occur no quicker than weekly. Doses greater than 5 mg daily should be administered in two divided doses. When discontinuing therapy, dosage reduction should occur gradually to avoid symptoms of withdrawal. Dosage adjustment is necessary in patients known to metabolize CYP2C19 poorly and in patients with mild or moderate hepatic impairment. No adjustment is required for mild or moderate renal impairment. No information is available for severe hepatic or renal impairment. Clobazam can be taken without regard to meals, and tablets may be administered whole or crushed and mixed in applesauce.⁹

Comments

Somnolence and sedation were the most commonly reported adverse effects in clinical trials.^{7,8} These effects were reported at all effective doses and were dose related but may diminish over time with continued treatment. Other common adverse effects occurring in greater than 5% of patients are pyrexia, lethargy, drooling, aggression, vomiting, constipation, fatigue, sedation, ataxia, insomnia, and cough. As with other antiepileptic drugs, clobazam can increase the risk of suicidal thoughts or behaviors.⁹ Severe skin reactions and/or rashes were not noted during clinical trials, which may provide an advantage of using this drug over another agent. However, there have been a few reports outside the United States prior to Food and Drug Administration (FDA) approval. Incidence and causality cannot be determined at this time.⁷

Table 1. *Erwinia* Asparaginase Dose Conversion

Asparaginase Product	Substitute Dose
Pegaspargase	25,000 International units/m ² three times per week, for 6 doses for each scheduled dose of pegaspargase
<i>E coli</i> asparaginase	25,000 International units/m ² for each scheduled dose of <i>E coli</i> asparaginase

ERWINIA ASPARAGINASE (ERWINAZE); APPROVAL NOVEMBER 18, 2011

Asparaginase is an important component of multidrug induction, consolidation, and continuation therapy for acute lymphocytic leukemia (ALL). Asparaginase is an enzyme derived from *Escherichia coli* and *Erwinia chrysanthemi*. A third product is also available, pegaspargase, as a polyethylene glycol conjugate of *E coli* asparaginase. *E coli* asparaginase is considered first-line therapy for many ALL treatment protocols. Unfortunately, approximately one-third of patients will develop an allergic reaction to *E coli*-derived asparaginase, necessitating a switch to an alternative asparaginase product.¹⁰ Once a patient has an allergic reaction to *E coli* asparaginase, they are typically switched to asparaginase *Erwinia chrysanthemi* (Erwinaze, EUSA Pharma (USA), Inc., Langhorne, PA). Most patients will tolerate the switch, with 75% of patients completing their scheduled therapy.¹¹

Indication(s)

Erwinia asparaginase is used in the treatment of patients with ALL who have developed hypersensitivity to *E coli*-derived asparaginase. Two randomized studies have demonstrated lower event-free survival with *Erwinia* asparaginase than *E coli* asparaginase.^{12,13} It is important to note the doses for the two products were the same in both studies and were not adjusted for *Erwinia* asparaginase's shorter half-life.

Clinical Pharmacology

Erwinia asparaginase is an asparagine-specific enzyme that catalyzes the hydrolysis of asparagine to aspartic acid and ammonia. Asparaginase takes advantage of the inability of leukemia cells to *de novo* synthesize the non-essential amino acid asparagine, thus depending on circulating asparagine to meet metabolic needs. Normal cells are able to make their own asparagine.

There are significant differences in the elimination half-lives of the three formulations adminis-

tered intramuscularly: *E coli* asparaginase, 26 to 30 hours; pegaspargase, 5.5 to 7 days; and *Erwinia* asparaginase, 16 hours.¹⁴ *Erwinia* asparaginase has a more rapid elimination and may require more frequent drug administration.¹⁵ Pharmacokinetics for *Erwinia* asparaginase have not been well defined. Serum trough concentrations were evaluated in 48 pediatric ALL patients ≥ 2 to ≤ 18 years old following administration of *Erwinia* asparaginase, 25,000 international units/m², intramuscularly, three times weekly for six doses. All patients achieved serum trough asparaginase concentrations of ≥ 0.1 international units/mL at either 48 hours or 72 hours after the third dose. This serum trough concentration correlates with asparagine depletion and serum levels, associated with clinical efficacy. No formal studies have evaluated drug interactions with *Erwinia* asparaginase and other medications.⁹

Dosage and Administration

Erwinia asparaginase is available as a lyophilized powder in single-use vials containing 10,000 international units. Contents of the vial are reconstituted with 1 or 2 mL of preservative-free normal saline. Reconstituted solution should be administered within 4 hours of preparation. The solution should not be frozen or stored in the refrigerator. The usual recommended dose of *Erwinia* asparaginase is 25,000 international units/m² administered intramuscularly for each scheduled dose of *E coli* asparaginase (Table 1). When substituting for the dose of pegaspargase, *Erwinia* asparaginase, 25,000 international units/m², is administered intramuscularly three times a week for six doses for each planned dose of pegaspargase.

Comments

Hypersensitivity reactions have been reported in 17% of patients who were switched to *Erwinia* asparaginase following hypersensitivity reactions to either *E coli* asparaginase or pegaspargase.¹¹ In a randomized study, *Erwinia* asparaginase had less than half the allergic reaction rate compared to that of *E coli* asparaginase.¹³ In addition,

coagulation abnormalities were lower in patients treated with *Erwinia* asparaginase than with *E coli* asparaginase.¹³ *Erwinia* asparaginase is also associated with lower antibody formation, which has been associated with reduced drug activity.¹⁴ Other adverse effects include pancreatitis (4%), liver abnormalities (4%), coagulation abnormalities (3%), hyperglycemia (2%), and nausea and vomiting (2%). Side effects reported in 1% of recipients included headache, abdominal pain, diarrhea, and seizures.¹¹

GLUCARPIDASE (VORAXAZE); APPROVAL JANUARY 17, 2012

Methotrexate is one of the most widely used chemotherapy agents and can be administered over a wide dosage range. High-dose methotrexate (≥ 1000 mg/m²) is used in combination with leucovorin rescue. Methotrexate is eliminated primarily (~90%) by renal excretion. High-dose methotrexate requires vigorous intravenous fluid hydration and urinary alkalization to enhance methotrexate urinary solubility and renal excretion. A small percentage of patients will develop methotrexate-induced nephrotoxicity caused by precipitation of methotrexate and its metabolites in the renal tubules. This can result in delayed methotrexate clearance, which increases the risk for systemic toxicities. Conventional treatment of methotrexate-induced nephrotoxicity includes supportive care with hydration and alkalization and pharmacokinetic-directed leucovorin rescue.¹⁶ There are also reports of the use of several dialysis procedures with various degrees of success in methotrexate removal. The recombinant bacterial enzyme glucarpidase (Voraxaze, BTG, Brentwood, TN), carboxypeptidase-G₂, is available to hydrolyze methotrexate into inactive metabolites. Glucarpidase (glucarpidase (Voraxaze, BTG, Brentwood, TN) a carboxypeptidase-G₂, is produced by recombinant DNA technology in genetically modified *Escherichia coli*. It is a 390-amino acid homodimer protein.

Indication(s)

Glucarpidase is indicated for the treatment of patients with toxic plasma methotrexate concentrations (>1 micromole/L) and delayed methotrexate clearance due to impaired renal impairment. Efficacy of glucarpidase was established in a subset of 22 patients who were part

Figure 3. Mechanism of action of Glucarpidase.

Methotrexate is converted to its inactive metabolites 2,4-diamino-N¹⁰-methylpteroic acid (DAMPA) and glutamic acid, providing an alternate route of elimination to renal excretion.

of a single arm, open-label, multicenter trial of patients with markedly delayed methotrexate clearance secondary to renal dysfunction. All these patients had a $>95\%$ reduction in methotrexate concentrations. Of this subset, 12 were patients ranging in age from 5 to 16 years old.¹⁷

The ability to resume large-dose methotrexate therapy after receiving glucarpidase for acute kidney injury and delayed methotrexate elimination was retrospectively reviewed in 20 patients.¹⁸ Thirteen of the 20 patients were able to resume high-dose methotrexate therapy at 50% to 100% of the recommended dose, 2 patients completed their planned methotrexate therapy, and 5 patients were not rechallenged. Eleven of the 13 patients tolerated the resumption of high-dose methotrexate therapy; 1 experienced renal toxicity with delayed methotrexate elimination, and another experienced neurotoxicity.

Clinical Pharmacology

Glucarpidase is a recombinant bacterial enzyme that hydrolytically removes the carboxyl-terminal glutamate residue from extracellular methotrexate, producing the inactive metabolites 4-deoxy-4-amino-N¹⁰-methylpteroic acid (DAMPA) and glutamic acid (Figure 3). DAMPA

and glutamic acid are then metabolized by the liver, providing an alternate route of methotrexate elimination in patients with impaired renal function. Glucarpidase does not affect intracellular methotrexate concentration.

The pharmacokinetics of glucarpidase were studied in 8 healthy subjects who were methotrexate naïve. One glucarpidase dose of 50 units/kg was administered and resulted in a mean elimination half-life of 5.6 hours, a mean peak plasma concentration of 3.3 mcg/mL, and a mean volume of distribution of 3.6 L. In 4 subjects with severe renal impairment ($\text{CrCl} < 30 \text{ mL/min}$), the mean pharmacokinetic parameters were similar except for a longer elimination half-life of 8.2 hours.¹⁷

Dosage and Administration

Glucarpidase is available as a lyophilized powder in single-use vials containing 1000 units of drug. The contents of the vial are reconstituted with 1 mL of normal saline. The reconstituted solution should be used immediately or stored under refrigeration (2-8°C) for up to 4 hours if not used immediately. The recommended dose is 50 units/kg administered as a single dose intravenously over 5 minutes. Limited evaluation of a second dose of glucarpidase has not been shown to be effective.¹⁷

Comments

Safety data are available from a study of 147 patients ranging in age from 1 month to 17 years old enrolled in two single-arm open-label unpublished studies.¹⁷ The most common adverse effects occurring in 2% of patients were paresthesias, flushing, and nausea and vomiting. Adverse effects occurring in $\leq 1\%$ of patients were headache, hypotension, hypersensitivity, rash and hypertension. Antibodies to glucarpidase were reported in 17% of patients. Leucovorin is also a substrate for glucarpidase and should not be administered within 2 hours before or after the administration of glucarpidase.

IVACAFTOR (KALYDECO); APPROVAL JANUARY 31, 2012

Cystic fibrosis (CF) is the result of mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. These mutations result in alterations in the quantity or function

of *CFTR* protein in the cell membrane. The *CFTR* protein is an epithelial ion channel that regulates chloride and water transport in various tissues and organs. One mutation, G551D, impairs the ability of the *CFTR* to open. Ivacaftor (Kalydeco, Vertex, Cambridge, MA) is a drug that increases the amount of time the *CFTR* channel remains open, which potentiates chloride transport.

Indication(s)

Ivacaftor is indicated for the treatment of cystic fibrosis in patients ages 6 years and older who have a G551D mutation in the *CFTR* gene (G551D-*CFTR*). The safety and efficacy of ivacaftor has been established in two clinical trials. The first trial included 161 CF patients ≥ 12 years old randomized 1:1 to receive either ivacaftor, 150 mg twice daily, or placebo. Ivacaftor resulted in significant improvement in predicted forced expiratory volume in 1 second (FEV_1) of 10.6% over placebo from baseline to week 24 and was maintained for 48 weeks.¹⁹ The second study included 52 patients (6-11 years old) randomized 1:1 to receive either ivacaftor, 150 mg twice daily, or placebo. Similar findings were seen (12.5% improvement in FEV_1) at 24 weeks that persisted through week 48.²⁰

Clinical Pharmacology

Ivacaftor acts on the malfunctioning *CFTR* protein on the cell surface of epithelial cells, resulting in a more effective opening of the *CFTR* chloride channel. *In vitro*, ivacaftor increases *CFTR*-mediated chloride transport, measured by increased transepithelial current in rat cells expressing G551D-*CFTR* protein. A similar increase was noted in human bronchial epithelial cells expressing G551D-*CFTR* protein.²¹

The pharmacodynamic effects of ivacaftor demonstrate significant reduction in sweat chloride concentrations in patients with the *CFTR* gene carrying the G551D mutation.

Following oral administration, peak plasma concentration occurs at approximately 4 hours. Absorption is increased 2- to 4-fold when given with a high-fat meal. Protein binding is approximately 99%, primarily to α -1 acid glycoprotein and albumin. The mean apparent volume of distribution is approximately 353 L. Ivacaftor is extensively metabolized, primarily by CYP3A. Caution should be taken when administering this drug concomitantly with moderate and strong

Table 2. Ivacaftor Dosage Adjustment Recommendations

Reason	Dosage Adjustment
Child-Pugh class A (mild hepatic impairment)	No adjustment necessary.
Child-Pugh class B (moderate hepatic impairment)	Decrease dose to 150 mg once daily
Child-Pugh class C (severe hepatic impairment)	Use cautiously; consider decreasing to 150 mg once daily or less often
Coadministration with moderate CYP3A inhibitor	Decrease dose to 150 mg once daily
Coadministration with strong CYP3A inhibitor	Decrease dose to 150 mg twice weekly

CYP3A inhibitors, and food containing grapefruit and Seville oranges should be avoided. The M1 metabolite has approximately 1/6 the potency of ivacaftor and the M6 metabolite approximately 1/50 the potency. Most of the ivacaftor is eliminated in the feces after metabolic conversion. There is negligible urinary excretion of the unchanged parent compound. The elimination half-life is approximately 12 hours. Steady-state is reached in 3 to 5 days with an accumulation factor ranging from 2.2- to 2.9-fold when dosage is every 12 hours. Patients with moderately impaired hepatic function (Child-Pugh class B) have a 2-fold increase in AUC compared to healthy subjects. Altered renal function is not expected to have a significant effect on ivacaftor.

Dosage and Administration

Ivacaftor is available as a light-blue film-coated capsule-shaped 150-mg tablet. The recommended dosage for patients ≥ 6 years old is one 150-mg tablet taken orally every 12 hours with a fat-containing meal.²⁰ Patients with hepatic impairment or concomitant therapy with CYP3A inhibitors require dosage adjustments (Table 2).¹⁹ No information is available regarding crushing, splitting, or administering tablets via an enteral feeding tube.

Comments

The most common adverse effects occurring in greater than 5% of patients are headache, upper respiratory infection, nasal congestion, nausea, rash, rhinitis, dizziness, and arthralgia.²⁰ Elevated transaminases have been reported in patients with CF receiving ivacaftor; therefore, it is recommended that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) be assessed prior to starting therapy, then every 3 months for the first year of treatment, and annually thereafter. Dosing should be interrupted for patients with AST or ALT values greater than five times the upper limit of normal. Ivacaftor should

not be used in patients who are homozygous for the F508del mutation in the *CFTR* gene as efficacy was not shown to be different compared to placebo in these patients.¹⁹

SPINOSAD (NATROBA); APPROVAL JANUARY 18, 2011

Head lice infestation, or pediculosis capitis, is seen most commonly in children ages 3 to 12 years old.^{22,23} According to the American Academy of Pediatrics, first-line treatment for head lice is over-the-counter (OTC) permethrin, unless resistance has been proven in the community. Other products such as benzyl alcohol or malathion may be considered if a patient has demonstrated resistance or has failed to respond to initial therapy.²³ Spinosad (Natroba, Insight Pharmaceuticals, Carmel, IN) is a newly approved topical prescription medication that has shown to be more effective than permethrin in recent studies.²⁴

Indication(s)

Spinosad is used as topical treatment of head lice infestations in patients 4 years of age and older. It should be used in conjunction with other lice management techniques including appropriate sterilization and cleaning of recently used clothing, bedding, towels, and personal care products.²⁵

In a report from two multicenter, investigator-blinded, controlled trials, efficacy was significantly better for spinosad (84.6% and 86.7%) than for permethrin (44.9% and 42.9%). Also, the patients receiving spinosad had significantly lower incidence of need for repeated treatment (36.2% and 13.8%) than the patients who received permethrin (64.5% and 60.3%).²⁴

Clinical Pharmacology

Spinosad is a 5 to 1 mixture of spinosyn A and

Figure 4. Chemical structures of spinosyn A and spinosyn D.

spinosyn D, respectively (Figure 4). Compared to other insecticides, spinosad has a unique mechanism of action in which it alters nicotinic and gamma-aminobutyric acid receptor function.^{26,27} This leads to neuronal excitation, involuntary muscle contraction, and periods of hyperexcitation, which ultimately causes paralysis and death of the lice.^{25,28} One of the challenges with insecticides that affect the nervous system is that they are not active against larvae early in development. This is because they do not yet have intact nervous systems. One of the proposed advantages of spinosad is that it is not significantly metabolized and may be present longer to act against larvae once their nervous systems do develop.^{26,27} This could potentially decrease the need for multiple treatments.

Data suggest spinosad is not expected to be systemically absorbed with topical administration, but because the commercially available product contains benzyl alcohol, it should not be used in patients younger than 6 months old.²⁵ Large amounts of benzyl alcohol can result in a fatal toxicity in neonates called “gasping syndrome,” which is associated with metabolic acidosis, respiratory distress, CNS dysfunction, hypotension, and cardiovascular collapse. There is no information available regarding the potential for drug interactions.

Dosage and Administration

Spinosad is available only as a topical suspension and is not for oral use. Prior to administration, it is important to shake the bottle well. The

suspension is first applied to the scalp and then spread to cover dry hair for 10 minutes, then rinsed off thoroughly with warm water. The use of a nit comb is not required because of the drug’s ovicidal activity. A second treatment should be applied after 7 days if lice are still present.²⁵

Comments

The most common adverse effects in clinical trials were scalp and ocular irritation and erythema, but overall, spinosad was well tolerated.²⁴ Spinosad appears to be an efficacious treatment option based on available literature, but use may be limited by cost and prescription-only availability. Future studies comparing the safety and efficacy of spinosad to second-line agents such as malathion or benzyl alcohol would be beneficial in determining spinosad’s place in therapy.²⁸

TOCILIZUMAB (ACTEMRA); APPROVAL APRIL 15, 2011

Systemic juvenile idiopathic arthritis (SJIA) is an orphan disease that is systemic and inflammatory in nature. It generally has a chronic course and is clinically distinguishable from other forms of juvenile idiopathic arthritis by the presence of fevers, skin rash, lymphadenopathy, and serositis. Cases can be monocyclic, cycles of relapse-recurrence, or continuous.²⁹

Indication(s)

Actemra (Genentech, Inc., San Francisco, CA) was approved for adult patients with rheuma-

toid arthritis was granted in 2010, and approval for SJIA in patients 2 years of age and older was granted in 2011. It may be used alone or in conjunction with methotrexate.³⁰ Approval was based on a phase 3, 12-week, randomized, blinded, placebo-controlled study in 56 patients who completed the open-label phase. There were 44 patients randomized to undergo the blinded phase (20 received tocilizumab, 23 received placebo, and 1 withdrew).³¹ The primary endpoint was an American College of Rheumatology Pediatric 30 response, defined as 30% improvement in a minimum of three variables with worsening of no more than one variable by more than 30% when evaluating improvement or progression of disease and a C-reactive protein concentration of less than 15 mg/L.³² Eighty percent of treated patients maintained this primary endpoint compared to 17% of patients receiving placebo.³¹

Clinical Pharmacology

Tocilizumab is a humanized monoclonal antibody that binds to interleukin-6 (IL-6) receptors, thus inhibiting IL-6 signaling. IL-6 is a proinflammatory cytokine produced by a number of immune cells including B and T cells, lymphocytes, monocytes, and fibroblasts (Figure 5).³⁰ The elimination half-life is dose-dependent: 11 days for the 4 mg/kg dose and 13 days for the 8 mg/kg dose and up to 23 days in pediatric patients with SJIA. The accumulation factor is approximately 3 after 12 weeks of therapy with dosing every 2 weeks. Tocilizumab has the potential to cause interactions with CYP450 substrates, especially CYP2C19 and CYP3A4. These interactions may be clinically relevant in drugs with a narrow therapeutic index or where a decrease in effectiveness would be unfavorable.²⁸

Dosage

Tocilizumab is available as a sterile, preservative-free solution for intravenous infusion at a concentration of 20 mg/mL in single-use vials containing either 80 mg in 4 mL, 200 mg in 10 mL, or 400 mg in 20 mL. In patients weighing <30 kg, the dose is 12 mg/kg every 2 weeks as a 60-minute infusion diluted to a final volume of 50 mL using normal saline. In patients weighing ≥30 kg, the recommended dose is 8 mg/kg every 2 weeks as a 60-minute infusion.³⁰ This tocilizumab dose is diluted to a final volume of 100 mL using normal saline.

Figure 5. Mechanism of action of tocilizumab.

Comments

The adverse reactions most commonly reported (5% or greater) were upper respiratory tract infections, nasopharyngitis, headache, hypertension, and increased ALT. Tocilizumab should not be given during an active infection. Caution should be used in patients who have an elevated risk of gastrointestinal perforation. Laboratory monitoring recommendations include neutrophils, platelets, lipid profile, and liver function tests. Live vaccines should not be administered concurrently in a patient being treated with tocilizumab. Patients should also be evaluated for latent tuberculosis before therapy is initiated and during therapy. Dosing modifications may be necessary if the patient develops liver enzyme abnormalities, low absolute neutrophil counts, or low platelet counts.³⁰

Hypersensitivity reactions, including anaphylaxis, is rare (<1%). Premedication is not required prior to administration. There has been a single report in the postmarketing setting of a patient who had previously experienced an infusion related reaction and received pretreatment with steroids and antihistamines prior to the next infusion. This patient experienced fatal anaphylaxis despite premedication during this subsequent exposure to tocilizumab. It is recommended that patients who develop hypersensitivity reactions during tocilizumab infusion should have prompt discontinuation and not be rechallenged.²⁸

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ACKNOWLEDGMENT Figure 1 is a photo licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. Attributed to Musides at en.wikipedia. <http://en.wikipedia.org/wiki/File:Bbasgen-scorpion-front.jpg> Accessed September 22, 2012.

ABBREVIATIONS ALL, acute lymphocytic leukemia; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area-under-the concentration curve; BPCA, Best Pharmaceuticals for Children Act; CFTR, cystic fibrosis transmembrane conductance regulator; CNS, central nervous system; DAMPA, 4-deoxy-4-amino-*N*¹⁰-methylpterotic acid; FDA, Food and Drug Administration; GABA, γ-aminobutyric acid; LGS, Lennox-Gastaut syndrome; PREA, Pediatric Research Equity Act; SJIA, systemic juvenile idiopathic arthritis

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