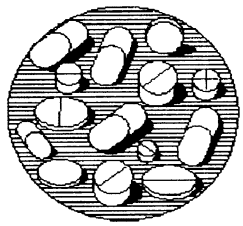
OREGON DUR BOARD NEWSLETTER



Vol. 1 No. 3 February 1999

Oral Diabetic Agents Reviewed

by: Terri Bianco, Pharm. D.

Until recently, patients with Type 2 diabetes mellitus had few options for management of their disease. Sulfonylureas were the only orally available agents. Those patients who failed to respond were left with insulin as the single alternative, and the issue of whether tight glycemic control was beneficial in the Type 2 diabetic patient was unresolved. New options for oral management of diabetes mellitus have emerged, and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that lowering blood glucose can reduce the progression of diabetes complications. [1,2] This article will compare the current options for oral drug therapy of Type 2 diabetes mellitus.

SULFONYLUREAS act by stimulating pancreatic beta-cell insulin release. They differ in duration of action and somewhat in side effect profile. They are effective in reducing HbA1C by 1.5-2.0% and controlling fasting plasma glucose in approximately 50% of patients. Unfortunately, secondary failure rates are high. Approximately 3 to 5% of patients per year who initially respond to sulfonylureas subsequently stop responding to the drugs. As the ability of the pancreas to produce insulin is required for efficacy, these agents are most beneficial in patients with early disease. Predictors of good response include: 40 years or more of age at onset, with disease less than 5 years and a FPG of less than 300 mg/dL.

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Citalopram (Celexa®): A New Drug for Depression

by: Kyle Kojiro, Pharm.D. Candidate
Dean Haxby, Pharm.D.

Citalopram (Celexa®) is a new selective serotonin re-uptake inhibitor (SSRI) that has recently become available in the United States for the treatment of depression. It has been available in other countries for nearly a decade and is widely used in a number of European countries. This article reviews citalopram and compares it to other antidepressants.

Pharmacology: Citalopram exhibits greater selectivity for inhibiting serotonin re-uptake versus norepinephrine re-uptake compared to fluoxetine, paroxetine and sertraline. However there is little evidence to suggest that this greater selectivity translates into an improved clinical profile.

Pharmacokinetics: Table 1 compares the pharmacokinetic profile of citalopram to other SSRIs. Following oral administration, citalopram is completely absorbed in the gut with peak plasma concentrations achieved in 2 to 4 hours. Food has minimal effect on absorption. All SSRI's are administered on a once daily basis.

Table 1: Pharmacokinetic Comparisons of SSRIs.

SSRI	t1/2 (hrs)	Plasma Protein Binding (%)	Meta-bolism	Active Meta-bolism	Excre-tion ◆
Fluoxetine	84	95	Liver	Yes	R
Sertraline	26	99	Liver	Yes*	R/F
Paroxetine	21	95	Liver	No	R
Citalopram	**33**	**50-80**	**Liver**	**Yes***	**R/F**

*Not clinically significant ◆ R = Renal F = Fecal

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New Treatment for Chronic Hepatitis C Infection Examined

by: Susan Raber, Pharm.D.

Hepatitis C virus (HCV), formerly known as non-A, non-B hepatitis, has become a major public health concern and a focus of recent media attention. It wasn't until 1989 that the virus was identified through modern techniques of molecular cloning.[1] The Centers for Disease Control and Prevention (CDC) now estimate that approximately 4 million Americans are chronically infected with the hepatitis C virus while over 200 million are infected worldwide.[2] However, many more may unknowingly be infected since most will remain relatively asymptomatic.

Chronic HCV is a disease of decades, progressing slowly over the first and second decade after infection to cirrhosis in 15 to 20%, hepatocellular carcinoma in 1 to 4%, and ultimately to death in 8,000 to 10,000 people in the U.S. per year.[1] These complications now place hepatitis C as one of the leading indications for liver transplantation.

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Citalopram (Celaxa®), continued from page 1

Clinical Trials: In comparative trials with imipramine, citalopram showed superior tolerability and was found to be similar at decreasing or eliminating depressive symptoms assessed by the Hamilton Depression Scale (HAMD) and Montgomery-Asberg Depression Rating Scale (MADRS). [1,2,3]

A few trials have compared citalopram with other SSRIs. No significant differences in efficacy or tolerability were found between the two treatment groups. [4,5]

Preliminary studies suggest that citalopram may be effective in OCD panic disorder, alcoholism, social phobia, and emotional lability in post-stroke and Alzheimer disease patients. [6,7,8] Additional research is needed before citalopram can be recommended for the treatment of these conditions.

Drug-Drug Interactions: As with other SSRIs, concurrent use of monoamine oxidase inhibitors (MAOIs) or use within 2 weeks of discontinuation of MAOI is contraindicated due to the risk of serotonin syndrome. Cimetidine has been shown to reduce the clearance and increase blood level of citlopram.

Since CYP3A4 and CYP2C19 are the primary hepatic enzymes responsible for the metabolism of citalopram, levels may be increased by drugs which inhibit those enzymes. Studies have not been conducted with known inhibitors of these enzymes (e.g. ketoconazole, itraconazole, macrolike antibiotics, and omeprazole) the potential for interaction should be considered.

Table 2 compares the relative inhibitory potency of SSRIs at the CYP450 isoenzymes. Overall, citalopram compares favorably with other SSRI antidepressants and appears to have a low propensity to significantly inhibit various CYP450 isoenzymes and the metabolism of other drugs. Citalopram has been shown to increase the levels of metoprolol and desipramine, two drugs metabolized by CYP2D6. [9]

Table 2: Relative Potency of Inhibition of CYP450 Isoenzymes by Various SSRIs.

SSRI	1A2	2C9	2C19	2D6	3A3/4
Fluoxetine	0	+/++	+	+++	+
Sertraline	0	+	0	+	+
Paroxetine	0	0	0	+++	0
Citalopram	+	0	+	+	0

Key: 0=none, + = low, ++ = moderate, +++ = high

Adverse Reactions: Overall, the adverse effect profile of citalopram closely resembles that of the other SSRIs. The most common side effects include: nausea (21%), dry mouth (20%), somnolence (18%), insomnia (17%), sweating (11%), tremor (8%), and ejaculation failure (4%).

In overdose, toxicity produced with citalopram appears to be significantly less than that seen with TCA overdose. At doses of 600mg or less, symptoms produced are fairly mild and benign. [10] At higher doses, seizures can occur in about one third of cases. Prolongation of the QT interval is also common, but only one possible case of torsades de pointes has been described. [10] Twelve fatalities have been reported involving overdoses of citalopram, and 10 of these were in combination with other drugs and or alcohol. In the two cases involving citalopram alone, massive doses were taken (3920mg and 2800mg). [9]

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Table 3: Cost Comparisons of Selected Antidepressants

ANTIDEPRESSANT	USUAL DOSE (mg/day)	DOSING REGIMEN	COST PER YEAR*
Amitriptyline generic (Elavil®)	100-200	150mg qhs	25
Imipramine generic (Tofranil®)	100-200	3 x 50 mg qhs	66
Desipramine generic (Norpramin®)	100-200	2 x 75mg qhs	85
Trazodone (Desyrel®)	150-600	3 x 100mg qhs	107
Nortriptyline generic (Pamelor®)	50-150	2 x 50mg qhs	119
Citalopram (Celexa®)	**20-40**	**½ x 40mg qd** **1 x 20mg** **1 x 40mg qd**	**327** **628** **655**
Sertraline (Zoloft®)	50-100	½ x 100mg qd 1 x 50mg qd 1 x 100mg qd	370 720 740
Paroxetine (Paxil®)	20	½ x 40mg qd 1 x20mg qd	394 724
Nefazodone (Serzone®)	200-600	150mg bid	702
Mirtazapine (Remeron®)	15-45	15mg qhs	726
Venlafaxine (Effexor®)	75-375	75mg bid	797
Fluoxetine (Prozac®)	20	20mg qd	813
Bupropion SR (Wellbutrin SR®)	150-450	150mg bid	864

* Cost based on average wholesale price(AWP) - 11% or HCFA maximum allowable cost (MAC) from Drug Topics Redbook Update December 1998

Citalopram (Celexa®), continued from page 2

Dosing: Montgomery et al, conducted a meta-analysis to determine the optimal dosing regimen for citalopram. [11] Doses of 20mg and 40mg daily are effective. A subgroup analysis of patients with recurrent and severe depression indicated better response with 40mg daily than 20mg. Studies evaluating doses greater than 40mg daily suggest that there is not a significant therapeutic benefit from higher doses, but they were typically associated with more side effects. Therefore, doses above 40mg/day are generally not recommended.

The initial recommended dose is 20mg per day, and the dose may be increased to 40mg per day after an interval of not less than one week.[9] For patients with mild to moderate depression, the elderly, and those with hepatic impairment, a 4 week trial at 20mg/day can be tried before increasing the dose in non-responders. For maintenance therapy, limited data suggest that 20mg and 40mg of citalopram are equally effective.

Cost: Table 3 (on the previous page) provides comparative cost information for various drugs for depression. One way to reduce the cost of SSRI therapy is to have patients break tablets, and utilize ½ tablet doses of a higher strength when doses of Celexa 20mg, Zoloft 50mg, and Paxil 10 or 20mg are prescribed. Doing so reduces cost of therapy by nearly 50%.

Conclusions: Citalopram appears to be comparable to currently available SSRIs for the treatment of depression. The primary advantages are that it is10-20% less expensive than currently available SSRI antidepressants and it appears to have a relatively low propensity for major drug interactions. When the 20mg dose is used, breaking the scored 40mg tablets substantially reduces the cost of therapy. ■

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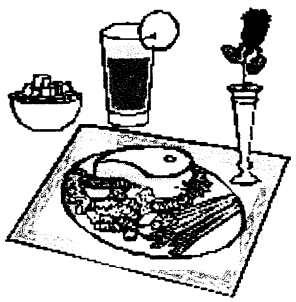
Hypoglycemia and a 1-3 kilogram weight gain are the two most common adverse effects. Hypoglycemia can be severe and prolonged. One study indicated that glimepiride was associated with fewer hypoglycemic events than glyburide. [3] Glyburide is metabolized to a renally eliminated active metabolite and should be avoided in the elderly and in patients with renal insufficiency. Sulfonylureas should be initiated at low doses and increased no more frequently than every one to two weeks. There is some evidence that the maximum effective doses of glyburide and glipizide are one-half the recommended maximum doses and that taking more than 10 and 20 mg daily, respectively, is not of benefit. Reserve the shorter acting agents for older patients.



METFORMIN (Glucophage®) is an antihyperglycemic agent. Its primary action appears to be decreasing glucose output by the liver, although it may have some peripheral insulin sensitizing activity. It may also decrease appetite and is the only antidiabetes medication which causes weight loss. Metformin is equally effective alone or in combination with sulfonylureas or insulin. It lowers HbA1C by 1.5 to 2.0%.

The most common adverse effects seen with metformin are belching, flatulence and diarrhea. These usually remit over time with continued therapy. Starting at a low dose and increasing gradually may diminish these effects. Dosage increases should be made no more frequently than weekly. Little additional anti-glycemic benefit is seen in doses above 2000 mg.

> The most significant adverse effect seen with metformin is lactic acidosis, which is fatal in 50% of cases.

The most significant adverse effect seen with metformin is lactic acidosis, which is fatal in 50% of cases. To minimize this risk, metformin is contraindicated in the presence of renal failure, congestive heart failure significant enough to require drug therapy, hepatic disease, alcohol abuse or any disorder which may increase the risk of lactic acidosis. It is also recommended that patients receiving iodinated contrast material have their metformin held at the time of the radiologic procedure and for 48 hours afterwards until renal function has been determined to be stable.

Metformin is eliminated by renal secretion, and should be avoided in patient with renal impairment. This has been defined as a serum creatinine of greater than 1.4 mg/dL in women and

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News Capsules

Pharmacy Use of 99999 Provider Numbers a Concern

The Oregon Drug Use Review (DUR) Council meets monthly to examine the drug therapy of Oregon Health Plan (OHP) patients. This review is mandated by the Health Care Financing Association and its purpose is to detect utilization patterns that may be outside current medical recommendations. The results of these reviews are often used for education purposes.

OMAP allows the use of 99999 provider numbers by dispensing pharmacies so as not to delay health service to OHP patients when the provider number is not known. However, the overuse of this number hinders the retrospective review process. The DUR Council needs the provider number to determine if a patient is seeing many providers and not disclosing all information to them. It is difficult for the DUR Council to put the pieces together without the provider information. Another use of the provider identification is to gather more information which may explain a particular utilization pattern.

OMAP will send a printout of providers and their numbers free of charge in order to update pharmacy databases. The list is organized by county and is available by calling 1-800-422-5047. If you need to determine a provider's number but do not want a list, call 1-800-336-6016, Monday- Friday during regular business hours.

New FDA Warnings: (http://www.fda.gov/cder/drug.htm)

- Cisapride and Serious Cardiac Arrhythmias: The labeling of Cisapride was changed June 26, 1998 to include a boxed warning regarding the potential for QT prolongation, torsades de pointes and sudden death when it is used in patients with associated risk factors or used in combination with drugs that also prolong the QT interval. It is contraindicated in patients that are taking drugs that inhibit cytochrome P450 3A4 (i.e. erythromycin, clarithromycin, troleandomycin, nefazodone, fluconazole, itraconazole ketoconazole, indinavir and ritonavir). This list is not complete for P450 3A4 inhibitors and includes only drugs listed in the labeling.
- Alcohol and OTC Pain Relievers: The FDA announced October 21, 1998 that all OTC pain relievers carry a warning label advising people who consume three or more alcoholic drinks daily to consult their doctors before using these drugs. The action follows public comment and recommendations of the Nonprescription Drugs Advisory Committee and the Arthritis Drugs Advisory Committee which concluded that chronic alcohol users should be warned that they may be at increased risk of liver damage or gastric bleeding from the use of these drugs.
- Tolcapone (Tasmar®) Warnings: The FDA released a warning November 16, 1998 advising doctors of a new finding of fatal liver injury associated with the use of tolcapone. The labeling now states that the drug should be reserved for use only in patients who have severe movement abnormalities and who don't respond to or who are not appropriate candidates for other available treatments. Three deaths have been reported from acute, severe liver failure. About 60,000 patients have been given tolcapone worldwide.
- Sildenafil (Viagra®) Labeling Revised: Revised in consultation with FDA on November 24, 1998, the new labeling is intended to help make sure that consumers and doctors are fully informed about the benefits and risks of using sildenafil, know that consideration must be given to the cardiovascular status of patients prior to prescribing sildenafil and know how to safely use the drug. The labeling notes that it is not possible at present to determine whether the cardiovascular events are directly related to sildenafil, to sexual activity, to the patient's underlying disease, or to a combination of these factors.

Dramatic Increase in Price of Generic Lorazepam and Chlorazepate Noted

The wholesale price of chlorazepate increased from $11.36/500 tablets to $377 in January. In March the wholesale price of lorazepam was increased from $7.30/500 tablets to $190. Figure 1 illustrates the effect this has had on the OMAP drug budget while utilization has remained flat. Other benzodiazepine options include:

- diazepam ($10.45 -23.25 /500)
- chlordiazepoxide ($15.75-18.55/500)
- alprazolam ($28.35-76.85/500)
- oxazepam ($29.65 - 44.65/500)

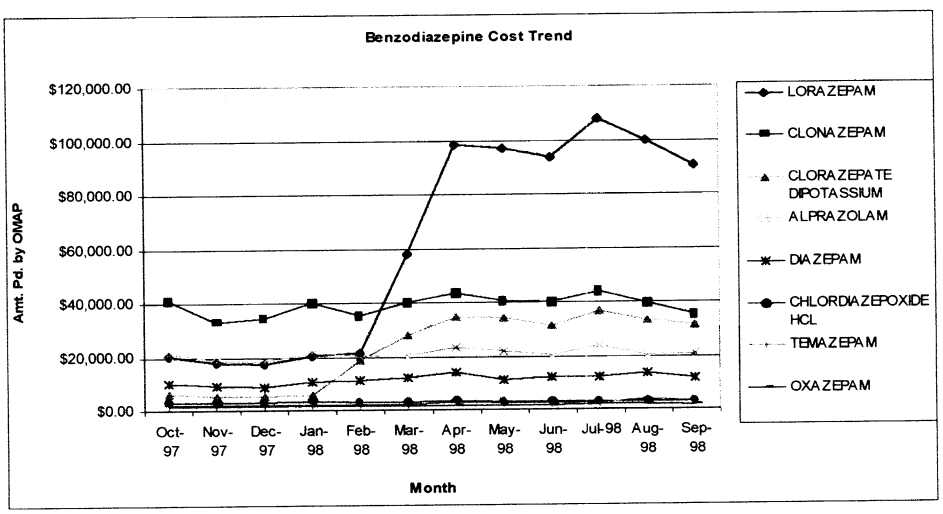

Figure 1

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1.5 mg/dL in men. Creatinine clearance should be measured in patients greater than age 80 years to accurately assess renal function.

Clinically significant drug interactions with metformin include cimetidine, which may decrease metformin clearance by impairing its renal tubular secretion. Acarbose can decrease metformin absorption. While hypoglycemia is very uncommon with monotherapy, it can occur when the drug is used in combination with sulfonylureas or insulin.

ACARBOSE (Precose®) is a glucosidase inhibitor which reduces the peak and rate of glucose absorption by the gut. The extent of absorption however is unchanged. This results in modest (0.5 - 1.0%) decreases in HbA1C. The adverse effects of acarbose are primarily gastrointestinal. Abdominal pain, flatulence, and diarrhea occur in many patients. Starting at a low dose of 25 mg daily, taken with the first bite of a meal, and increasing over a few weeks can increase tolerance. The maximum dose is 50 mg three times daily in patients under 60 kg and 100 mg three times daily in heavier individuals. Doses in excess of this have been associated with liver transaminase elevations. Acarbose may be useful in elderly patients, patients whose primary problems are large excursions in postprandial hyperglycemia, or those in whom modest reductions in HbA1C are warranted.

Hypoglycemia rarely occurs with acarbose monotherapy, but can occur when used in combination with sulfonylureas or insulin. Because acarbose blocks the absorption of sucrose, *hypoglycemia must be treated with dextrose.*

REPAGLINIDE (Prandin®) is a hypoglycemic agent which acts by stimulating pancreatic beta receptors to release insulin. The onset of effect of repaglinide is rapid and duration is short, hence it is administered with meals to stimulate meal-related insulin release. Only two trials of repaglinide have been published in manuscript form and its effects on HbA1C appear to be modest. [4,5] The need for multiple daily dosing may adversely influence compliance. In summary, the role of repaglinide in the management of diabetes mellitus is not yet well defined.

TROGLITAZONE (Rezulin®) is a thiazolinedione derivative that improves insulin utilization and glucose uptake. It can decrease plasma insulin concentrations, and has modest effects in decreasing blood pressure and plasma triglycerides. It can, however increase weight and LDL cholesterol. Anovulatory women with insulin resistance may have a return of ovulatory function with troglitazone treatment. It may be useful for insulin resistant, abdominally obese patients in combination with a sulfonylurea or insulin.

The onset of action may be seen in two to four weeks but maximum effects are not usually seen for six to eight weeks. The HbA1C lowering effects of troglitazone are typically more modest than seen with metformin and sulfonylureas, approximately 0.5-1% with monotherapy, but may be significantly greater (2.6%) in patients who are carefully selected for the presence of insulin resistance. It has been shown to allow reductions in the insulin dose of patients who are receiving high doses (>1u/kg/day) of insulin. When adding troglitazone to insulin therapy, hypoglycemia can occur. Patients should be instructed to monitor their CBGs and to decrease the insulin dose by 10-25% when their CBGs begin to fall.

The most significant adverse effect of troglitazone is idiosyncratic hepatotoxicity. In the United States, 26 liver related deaths and four liver transplants have been attributed to hepatic failure caused by the drug. It is currently recommended that hepatic transaminases be obtained at baseline, monthly for the first eight months of treatment, bimonthly for the remainder of the first year, and then periodically. Troglitazone therapy should not be initiated in patients with active liver disease or increased serum transaminase levels (ALT>1.5 times the upper limit of normal). If therapeutic efficacy is not seen within one month of achieving the maximum dose of the drug, it should be discontinued.

Troglitazone can induce the activity of the cytochrome P450 system. Its absorption may be reduced by concomitant administration with bile acid binding resins.

SUMMARY: Factors to be taken into consideration when deciding initial drug therapy for diabetes mellitus include duration of disease, baseline HbA1C, the presence of obesity and concurrent disorders, renal and hepatic function, and patient age.

Table 1: Diabetes Drug /Cost Per Year

DRUG	BRAND	USUAL DOSE	COST per YEAR ($)*
Glipizide	Generic	10 mg qd	23
glyburide	Generic	5 mg qd	175
micronized glyburide	Generic	3 mg qd	188
glipizide XL	Glucotrol XL®	10 mg qd	216
glimepiride	Amaryl®	4 mg qd	234
acarbose	Precose®	50 mg tid	480
metformin	Glucophage®	500 mg tid	550
repaglinide	Prandin®	4 mg tid	809
troglitazone	Rezulin®	400mg qd	1540

*Cost based on average wholesale price (AWP) - 11% or HCFA maximum allowable cost (MAC) in Drug Topics Redbook Update 12/98.

Sulfonylureas are still first line drug therapy for most patients with Type 2 diabetes mellitus. The most effective doses may be at half the maximum dose. Metformin may be considered as initial treatment for obese patients in the absence of contraindications. It may also be better tolerated than sulfonylureas in those patients whose HbA1C is less than 8.0%. For patients that do not respond to monotherapy with a sulfonylurea or metformin, combining these agents is often effective. Acarbose is useful as an adjunct to other agents, and may have a particular role in patients with significant postprandial glucose excursions or those in whom smaller reductions in glycosylated hemoglobin are needed. Troglitazone is expensive, has the potential for significant adverse effects, requires substantial monitoring of hepatic enzymes, and is less effective than sulfonylureas or metformin when used as monotherapy. It is best used in combination in patients taking high doses of insulin or sulfonylureas. The role of repaglinide has yet to be defined. ◘

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Hepatitis C, continued from page 1

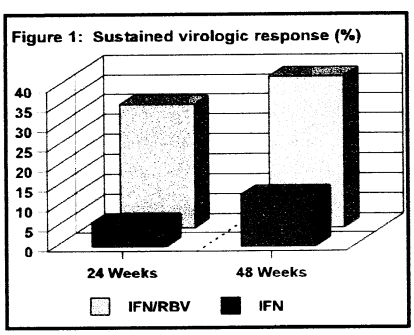
The cost for treating advanced liver disease and other symptoms of chronic infection can be substantial. The public health threat of hepatitis C lies in the fact that it is a transmissible blood-borne disease for which no vaccine and only minimally effective therapy are available.

The virus is an RNA virus of approximately 10,000 nucleotides. [1] Variability in the nucleotide sequence of HCV among isolates, resulting from viral mutations, led to subdivision of the viral group into genotypes. There are six different genotypes with genotypes 1a and 1b being the most predominant in the U.S.

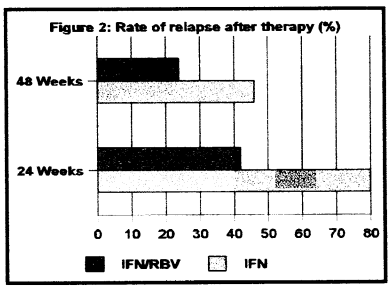
Until recently, the only treatment shown to have any efficacy against HCV was interferon alfa. Standard therapy of interferon alfa-2b (3 million units 3 times weekly for 6 to 12 months) results in disappearance of the virus from the bloodstream and normalization of serum aminotransferases by the end of therapy in close to 40% of patients.[1,3] However, over half of these patients who initially respond will relapse soon after stopping therapy leading to a sustained response rate of only 15 to 20%.
Factors most predictive of sustained response to interferon therapy include: genotypes other than 1 or 4, low levels of HCV RNA in serum prior to treatment, and presence of minimal to no hepatic fibrosis or cirrhosis.[1,3] Patients who are younger (<45 years old) or infected with the virus for <5 years also have a better chance of responding to interferon therapy. The NIH currently recommends treatment for patients with persistently elevated serum aminotransferases, HCV viremia, and findings of fibrosis and moderate inflammation on liver biopsy.[4]

Two large multicenter, randomized, controlled trials published recently show that combining interferon alfa-2b with ribavirin can increase sustained response rates in treatment naive patients as well as patients who have relapsed after demonstrating initial response to interferon monotherapy.[5,6] Ribavirin is a broad-spectrum oral antiviral. Against hepatitis C, it acts by reducing the viral-induced macrophage activation and therefore, inhibits induction of pro-inflammatory cytokines.[7] This immune modulation probably plays a greater role in its activity against HCV than its direct antiviral effects.

The study by McHutchinson et al. compared the combination of interferon and ribavirin with interferon alone for initial therapy of chronic hepatitis C in over 900 patients.[5] The primary endpoint of the study was sustained virologic response, defined as an absence of HCV RNA in the serum 24 weeks after treatment was completed.



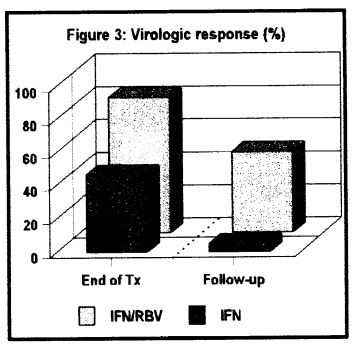
Secondary endpoints were normalization of serum aminotransferases and histologic improvement on liver biopsy. Results of sustained virologic response are summarized in Figure 1. Combination therapy was statistically superior to interferon alone regardless of duration of treatment. Interferon alone for 24 and 48 weeks resulted in sustained responses in 6% and 13% respectively, while combination therapy resulted in 31% and 38% sustained response rates respectively in the 24 and 48 week treatment groups. Although 48 weeks of combination treatment was statistically better than 24 weeks, further analysis of that group revealed that those patients infected with genotype 1 benefitted most from the extended duration of treatment.



The addition of ribavirin to interferon therapy reduced relapse rates by 50%, while extending the duration of therapy to 48 weeks also cut relapse rates in half (Figure 2).

The greatest predictors of response for this study was combination therapy with interferon and ribavirin, HCV genotype other than 1, baseline viral load less than 2 million, and absence of cirrhosis. For patients with a high baseline viral load infected with genotype 1, combination treatment for 48 weeks led to a better response. Unlike earlier studies of interferon alone, late clearance of the virus from the bloodstream (>4 weeks after start of therapy) was not predictive of treatment failure or relapse. In all 4 treatment groups, 23% to 59% of patients had virus detectable at 12 or 24 weeks into treatment yet still had subsequent sustained response.

Davis and his colleagues compared interferon alone with combination interferon and ribavirin in 345 patients with chronic hepatitis C who initially responded but then relapsed after completing a course of interferon therapy.[6] The proportions of the patients with genotype 1 or cirrhosis were lower than those expected in trials of initial therapy since patients with those characteristics are less likely to experience an initial response to interferon therapy. Virologic response, both at the end of therapy



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and 24 weeks after completing therapy, was statistically greater in the combination group (Figure 3). While 47% of the patients treated with interferon alone had virus absent by the end of treatment, only 5% remained undetectable at the end of follow-up.

In the combination group, 82% had virus absent by the end of treatment, and 49% maintained undetectable HCV RNA at the end of the 24-week follow-up. In contrast to the McHutchinson study, all patients who experienced a sustained virologic response in this study had HCV RNA undetectable before 12 weeks of treatment.

Again, the greatest predictor of sustained response in this study was treatment with combination therapy. However, in the combination therapy group, a sustained virologic response was significantly associated with baseline viral load of less than 2 million and a genotype other than 1. In the group treated with interferon alone, only a baseline viral load of less than 2 million was significantly associated with a sustained response.

Interferon alfa therapy is commonly associated with influenza-like symptoms, neurologic and emotional symptoms such as difficulty concentrating, anxiety, and depression, and hematologic side effects of thrombocytopenia, neutropenia, and anemia. [3] Ribavirin can accumulate in red blood cells and lead to hemolytic anemia which is reversible. [6] The incidence of side effects was higher after 48 weeks of treatment than after 24 weeks regardless of whether it was combination or monotherapy. The most common reason for discontinuing therapy in either of the studies was emotional disturbance, mainly depression, due to the interferon.

With the superior results of combination interferon and ribavirin therapy in each of the large, randomized studies, choice of therapy for patients with chronic hepatitis C should be re-evaluated. Addition of ribavirin to standard interferon therapy increased sustained response by 4-fold in treatment naive patients and nearly ten-fold in patients who relapsed after monotherapy. However, it remains to be determined whether or not the same magnitude of improved response will be realized in routine clinical practice. Patients must be highly motivated and compliant to maintain the treatment schedule and endure the side effects of therapy. This can be challenging without the close monitoring of a clinical trial.

The cost of therapy is high ranging from $6,400 to $8,600 for 24 weeks of combination therapy. Nonetheless, selection of patients for initial treatment should still follow the current NIH guidelines. Therapy should be offered to those with elevated serum aminotransferases, persistent HCV viremia, and presence of inflammation or fibrosis on liver biopsy. While genotyping was not recommended on a routine clinical basis previously, it may now be advantageous in selecting the duration of treatment since patients who benefitted most from 48 weeks of therapy were those with genotype 1. Evaluation of response at 12 weeks into therapy should also be reconsidered. Disappearance of HCV RNA from the serum by 12 weeks may no longer be predictive of sustained response in initial treatment of patients with combination therapy. ◘

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We hope you found this issue of the Oregon Drug Use Review Board Newsletter useful as well as thought-provoking and interesting.
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