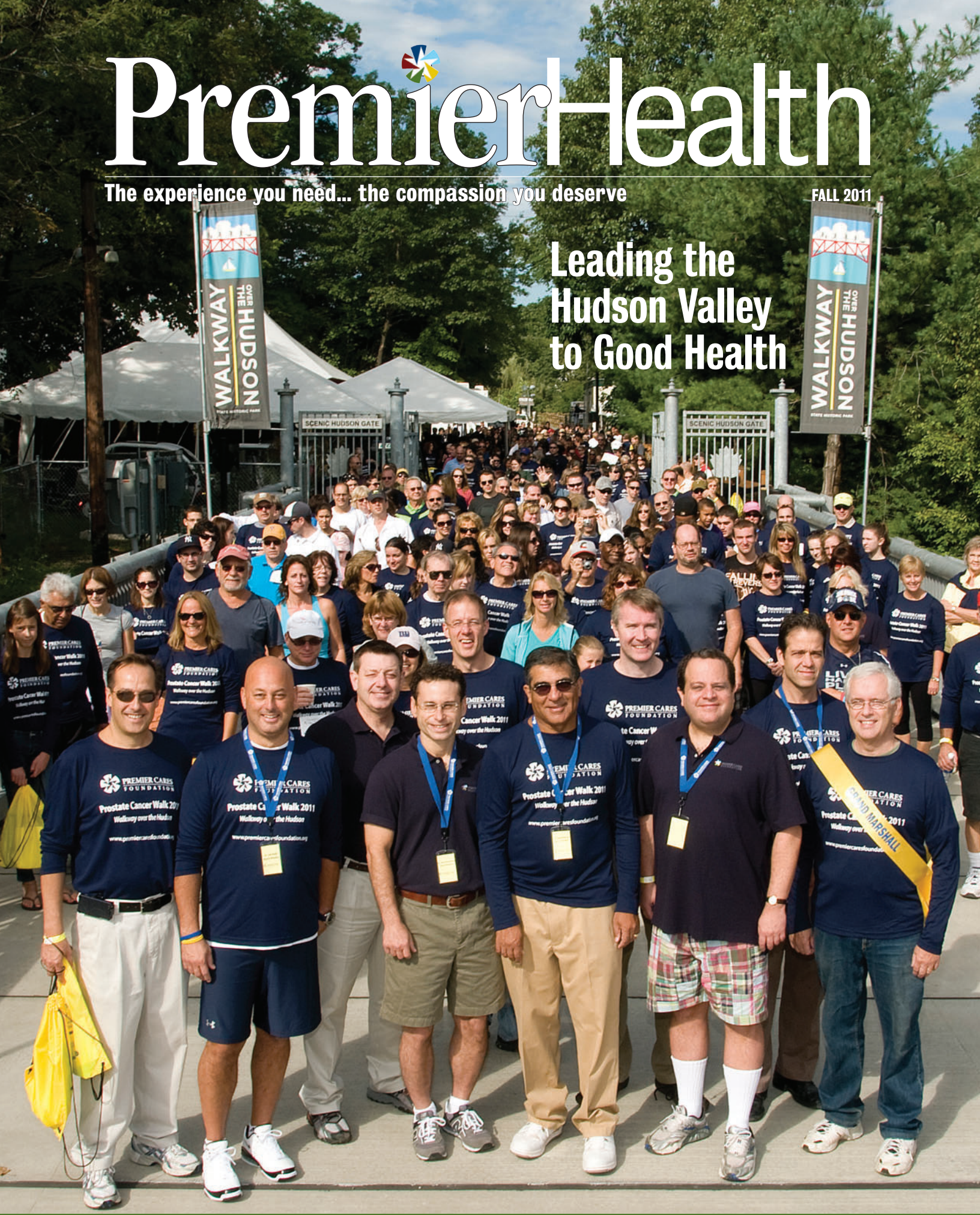
PremierHealth

The experience you need... the compassion you deserve

FALL 2011

Leading the Hudson Valley to Good Health



The magazine of PREMIER *medical group of the Hudson Valley*

LEADING THE WAY TO A HEALTHY HUDSON VALLEY

Premier Medical Group

Premier physicians in the lead *(left to right)*: Dr. Daniel Katz, Dr. Salvatore Buffa, Dr. Robert Dean, Dr. Jason Krumholtz, Dr. Paul Pietrow, Dr. Sunil Khurana, Dr. Walter Parker, Dr. Evan Goldfischer, Dr. Scott Kahn, and Grand Marshall Peter Scott.

This issue of Premier Health Magazine focuses on a number of breakthroughs in medical care in our region, some of which, we're proud to announce, are due to the work of Premier Medical Group physicians.

When Hudson Valley Urology and GI Associates got together, people wondered what sort of synergies would be gained, aside from the economies of scale that come from merging two large practices. We have found that there are many technologies that have crossed over between the two subspecialties and working together has been wonderful. Read about two examples of a real exchange of ideas that has resulted in real benefit to our patients in the report on new treatments for fecal incontinence (page 10) and for bile duct stones (page 13).

The physicians at GI Associates are very excited about two new medications for hepatitis C — read the article on page 4 to find out why.

And we are all excited about the first major event to be sponsored by the Premier Cares Foundation: September's Prostate Cancer Walk across the Walkway Over the Hudson was a resounding success. Not only did it spread awareneness about the disease, it raised funds to further the Foundation's work. Read the article about the Foundation (page 6) to find out what else is in store.

PREMIER *medical group*

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Northern Dutchess Hospital
St. Francis Hospital
St. Luke's Cornwall Hospital
Vassar Brothers Medical Center

A Robotic First for the Region

The region's first robot-assisted ureteral reimplant was recently performed by HVU's Dr. Naeem Rahman at Vassar Brothers Medical Center.

Urine travels from the kidneys to the bladder down two thin tubes called ureters, each about 8 to 10 inches long. Muscles in the ureter walls tighten and relax to force urine downward. Reimplantation is necessitated in adults by such conditions as pelvic cancers, fibrotic reactions, stone disease and, frequently, because of iatrogenic injuries.

The patient Dr. Rahman operated on had her right ureter injured in the course of a hysterectomy and she needed to use a nephrostomy tube to pass urine directly out of her kidneys. Using the da Vinci robot, Rahman was able to free up the ureter and reimplant it back into the bladder.

Urologists have actually been performing ureteral reimplants, using open surgery, for quite some time. A laparascopic approach to the procedure was introduced in 1994.

"The robotic approach allows us to work in small spaces," says Dr. Rahman. "Reimplanting a ureter requires lots of suturing, which is hard to accomplish laparascopically. It also gives great visibility to our working space which makes the robotic surgery, in my hands, easier than open surgery."

The robotic setup, according to Dr. Rahman, is identical to that for prostate surgery, in which he is expert. "It was a seamless transition," says Rahman. "The port placement and the direction the robot come into dock (from the feet of the patient) are almost identical to the approach for robotic prostatectomy."

From the perspective of the patient, robotic surgery means a faster recovery time and no large incisions. "The patient had 5 very small incisions, about the width of my index finger," says Rahman. "Her degree of pain was less and we were able to send her home the next day."

ADVANCING MEDICAL KNOWLEDGE

AT THE PODIUM AT THE AUA

In May of this year, Dr. Evan Goldfischer addressed a standing-room-only crowd at the annual meeting of the American Urological Association in Washington, DC. His podium session was devoted to discussion of (take a deep breath), "A multi-center, placebo-controlled trial investigating the safety and efficacy of once-daily tadalafil in men with signs and symptoms of benign prostatic hyperplasia taking concomitant A1-adrenergic antagonist therapy."

In layman's language that means "Is it safe to take Flomax for BPH at the same time you're taking Cialis for erectile dysfunction?"

"Many people who have erectile dysfunction (ED) also have BPH," explains Dr. Goldfischer. "Cialis, which is used to treat ED, is a type of drug called a vasodilator. It dilates your blood vessels, which is why some people who take it get light-headed or dizzy. Some of them also take Flomax, which relaxes the smooth muscle around the prostate, for BPH. But Flomax is also a basal dilator, which is why some people who take it get light-headed or dizzy.

"What do you do, as a urologist, if you have a patient with both ED and BPH and you prescibe them Cialis and Flomax? Will they get light-headed and dizzy? Will they get so lethargic they can't function?"

Many physicians have long prescribed BPH medications (alpha blockers) along with PDE5 inhibitors like Cialis to their patients. The original label for Cialis said patients had to wait at least 4 hours between taking the alpha-blocker and the PDE5 inhibitors. Subsequently, the label was changed to say men didn't have to wait, just be cautious. "Quite honestly," says Goldfischer, "though we've spoken about a possible interaction to our patients, I don't know that we were strictly monitoring them and asking about light-headedness and dizziness."

The study that Dr. Goldfischer's session elucidated was designed to test the safety of this common combination of drugs. Because the elderly respond differently to medications, the study specifically included a subgroup of men 75 and older.

The conclusion? The drugs don't have a compounding effect; men taking both drugs did not experience "treatment-emergent dizziness." That is, the combination is safe.

New Cures for Hepatitis C

Peter M. Varunok MD

"The message I want to send out to our patients and to the community is that this is a completely new era in the treatment of hepatitis C. With these newly approved drugs, we're in a position to cure the majority of people with hepatitis C and, in most cases, prevent them from progressing to cirrhosis and liver cancer.

I would encourage people with hepatitis C to call and make an appointment. We're reaching out to our existing patients in a systematic way. We want to make sure they're treated well, so we're putting updated support services—like side effects management and education—in place.

And I especially want to encourage people who have previously had treatment that wasn't successful to reconsider. Not only are the odds of being cured nearly twice as great as before, after only four weeks, testing can tell if a cure is likely and the rigors of treatment are worthwhile."

"We're very excited that we can offer these medications to patients," says Dr. Peter Varunok, "and improve their lives and give them the chance to make hepatitis C a thing of the past."

There are four things that people with hepatitis C, and those at risk of having the disease, need to know about teleprevir and boceprevir, the two drugs recently approved by the FDA.

1. Nearly 80 percent of previously untreated patients who add one of these medications to their drug regimen will be cured of hepatitis C. That makes the medications twice as effective as those previously available.

2. African-Americans—who did not respond well to the standard therapy—now have a better than 60 percent chance of a viral cure.

3. In many patients, the length of treatment will be half as long as previously (24 rather than 48 weeks).

4. After only four weeks, testing can reveal whether the treatment will be successful and merits completion.

These drugs, telaprevir (Incivek) and boceprevir (Victrelis), are of a type called protease inhibitors. They work directly on the hepatitis C virus, interfering with its reproduction. In the new drug regimen, one of these drugs will be added to the standard treatment of PEG interferon and ribavirin, anti-viral drugs that ramp up the immune system and immune response.

"Studies show an eradication rate of approximately 80 percent in people who have never been treated for hepatitis C," says Dr. Varunok, "and people whose previous treatments have been unsuccessful can approach this same rate. It's important to note that the responses in African-American is vastly improved over prior drug regimens."

In Dr. Varunok's view, one of the significant benefits of the new drug regimen is that after four weeks of treatment, it becomes clear whether or not the medication is going to work. "We base the course of therapy on how the patient responds early on," he says. "If they respond very quickly, the course of therapy can be as little as 24 weeks." The therapy typically requires intensive monitoring and multiple laboratory visits, so a shorter treatment schedule results in less disruption of the patients' daily life and fewer side effects.

With improved hepatitis C treatment now available, it makes more sense than ever for people at risk of infection to be tested. It's estimated that 70 percent of the 3.2 million Americans with hepatitis C don't know that they have it.

BATTLING PROSTATE CANCER...

What helps, what doesn't

BOOK REVIEW

Promoting Wellness for Prostate Cancer Patients

Dr. Mark A. Moyad, MD, MPH
(available on Amazon.com)

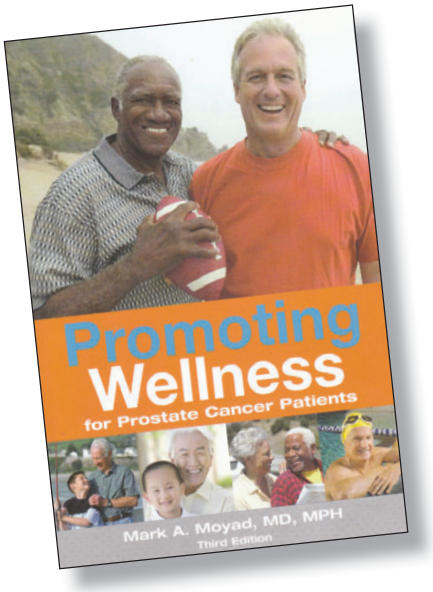
Many people these days are interested in holistic therapy, and just about everyone would prefer to take something "natural" rather than taking pills. When it comes to prostate cancer and prostate health, patients will ask, "What can I do doc, that's natural for it. Will saw palmetto or selenium be good for me?" All too often, the "cures" and supplements that patients are asking about have no scientific basis whatsoever. But they are being sold in vitamin shops or on the Internet.

The author of *Promoting Wellness for Prostate Cancer Patients*, Dr. Mark A. Moyad, is an internationally recognized authority on nutrition and supplement use for prostate cancer. As the Director of Preventive and Alternative Medicine at the University of Michigan Medical Center, he maintains an open mind regarding the beneficial possibilities. But as a physician and scientist, he is devoted to the facts rather than rumor, hope, or hype.

Heart Healthy = Prostate Healthy

Dr. Moyad's overriding message is that the most significant role for diet, nutritional supplements and herbs lies in the promotion of heart health. "Heart healthy equals prostate healthy," he writes, noting that, even among men diagnosed with and treated for prostate cancer, the number one cause of death is cardiovascular disease. "In addition," writes Moyad, "there is now plenty of clinical research to suggest that being heart healthy after being diagnosed with prostate cancer may actually increase the chances of beating prostate cancer itself."

The book takes a close, yet easy to grasp, look at a wide range of supplements related to the prostate. Regarding saw palmetto, one of the most popular herbal products for relief of BPH symptoms, Moyad is skeptical. The herb may artificially reduce PSA



blood levels (obscuring a cancer warning) and there is no evidence it does anything to prevent or treat prostate cancer. "The biggest problem," says Moyad, "is that the prescription medications for BPH work so well today… that it is difficult to ever consider recommending an herbal product over a drug …"

Considering the evidence on selenium, Moyad believes "there is no reason right now to take an individual selenium supplement." The largest clinical trial of the supplement has shown that, at the most common dosage, it does not prevent prostate cancer and may, in fact, increase the risk of type II diabetes. Most men will get all they need through a healthy diet or a multi-vitamin.

Dr. Moyad does find a number of supplements—such as ginger, ginseng and fish oil— to be helpful in the course of various treatments for prostate cancer and suggests sensible usages for them, for mitigating side-effects and increasing wellness. Aside from its focus on nutrition, the book provides a concise and useful overview of prostate cancer, from diagnosis through treatment.

Dr. Moyad's message is an important one. The information he provides will help people focus on things that are for real and help them save the money and effort they might invest in things that are useless.

Extending Lives

In April, 2011, the FDA approved Zytiga (abireterone acetate), a new drug to be used in the treatment of late-stage prostate cancer. In clinical trials, the drug prolonged the lives of men who had already received prior treatments, including chemotherapy, and had few available therapeutic options left.

In prostate cancer, the male sex hormone testosterone stimulates prostate tumors to grow. Drugs or surgery are used to reduce testosterone production or to block testosterone's effects. Sometimes, however, prostate cancer can continue to grow even when testosterone levels are low. Men with this type of the disease are said to have castration-resistant prostate cancer.

Zytiga, a once-daily tablet, further decreases production of testosterone that may be produced within the tumor. Not only does the drug extend survival, it also reduces pain and some of the other symptoms related to prostate cancer.

Premier Cares Foundation "Hits the Ground Running"

Julie Goldfischer, executive director of Premier Cares Foundation, addressing supporters at the Prostate Cancer Walk

Just months after becoming a fully accredited non-profit 501-(c) (3) corporation, Premier Cares Foundation has hit the ground running, putting an exciting agenda in place to further its mission of providing support, education and awareness relating to the prevention and treatment of urologic and digestive diseases. We couldn't have done it without our committed supporters in the Hudson Valley.

The physicians and health professionals of Premier Medical Group have formed Premier Cares Foundation to give back to the community in which they live.

In its first year, the Foundation is sponsoring events that provide education for health care providers and for the community at large. It is enabling free screening for prostate and colon cancer—the second and third most common cancers—for men and women who otherwise could not afford it.

The Foundation is working to provide treatment of prostate and colon cancer for uninsured patients who need help. It will be donating funds to St. Francis Hospital and Vassar Brothers Medical Center to help cover such costs.

And the Foundation is hard at work raising the funds necessary to implement its mission. The 2011 Prostate Cancer Walk raised over $120,000 to put back into the community.

The Foundation Agenda, So Far...

Annual Prostate Cancer Walk
Walkway Over The Hudson
September 10, 2011

The Foundation's signature public event for raising awareness and funds was a huge success, raising over $120,000. A look at the cover photograph of this magazine and the following two pages makes clear the enthusiasm and commitment of our physicians and the community.

Urology Teaching Day
Advancements in the treatment of urologic cancers / St. Francis Hospital
September, 2011

The target audience for this educational event includes oncologists, surgeons, urologists as well as primary care physicians, who often are the ones to initially diagnose urological cancer. In addition, the program reached out to oncology nurses, radiotherapeutic technicians, physician assistants and the general nursing community.

Topics covered include robotic surgery in radical prostatectomy, advances in radiation therapy and chemotherapy in the treatment of urologic cancers and an overview on "what works and what is worthless" among the fad diets and supplements promoted for prostate cancer patients.

"Typically, physicians and others are required to pay to attend continuing medical education (CME) credit programs," says Dr. Evan Goldfischer. "Our approach is that you shouldn't have to pay to get education. The Premier Cares Foundation is going to pay for everyone's CME and attendance. In turn, we would hope that there be some contributions to the foundation to further its programs."

Colon Cancer Awareness Day
March, 2012

Under the auspices of the Foundation, this effort to raise public awareness of colon cancer prevention will become a regular annual event.

In addition to educational programs, fund-raising and community participation, a number of free colonoscopies will be offered by the physicians of GI Associates, a division of Premier Medical Group.

Free Prostate Screenings
Benedictine Hospital; St. Francis Hospital; Vassar Brothers Medical Center
September, 2011

In the weeks before this Prostate Awareness Month program, men without health insurance or the needed financial means can come into St. Francis or Vassar Brothers to sign up for a free prostate exam, which will include a digital examination and PSA blood testing.

If a health concern is revealed, the Hudson Valley Urology physicians will counsel the patient on the next step. Funds raised by the Prostate Cancer walk will go towards paying for any further diagnostic or therapeutic actions needed, be it biopsy, surgery, radiation or chemo. The more money the Foundation raises, the more men can be helped.

Gastroenterology Teaching Day
Vassar Brothers Medical Center
September, 2011

GI Associates has been sponsoring a Gastroenterology Teaching Day in collaboration with the Vassar Brothers Medical Center CME department for at least a dozen years. Program director Dr. Sunil Khurana and his colleagues at GI Associates identify the topics they'd like to see discussed and suggest the medical authorities for each subject. Then, in concert with Michelle Palumbo, CME coordinator at Vassar, the program is put together.

GI Teaching Day is very well-attended, attracting up to 200 medical professionals annually. "We get great speakers," says Dr. Khurana. "For example, we've had Stephen Hanauer, the world authority on inflammatory bowel disease, ulcerative colitis and Crohn's disease give a talk. We normally have 5 speakers, with two topics which are very GI oriented, and three topics which will be attractive to general surgeons, internists and family doctors."

Topics for this year's Teaching Day included hepatitis C, probiotics and prebiotics, Barrett's esophagus, GIST, and hepatic encephalopathy.

Discussions are underway regarding sponsorship of next year's event by Premier Cares Foundation.

FUNDRAISER!

Walter Scheib, "The American Chef" and an American President

For 11 years, Walter Scheib cooked for the Presidents of the United States.

Tonight, he will cook for you.

Saturday, November 5, 2011
Poughkeepsie Tennis Club

Chef Scheib will prepare a delicious multi-course White House dinner, featuring an evening of the favorite dishes served during his tenure at the White House. Chef Scheib will fascinate you with White House insider's tales and culinary insights. This is your chance to be part of history and to feast like the presidents.

All proceeds will go to support the Premier Cares Foundation.

There may still be time to register. Contact:
Julie Goldfischer,
Executive Director,
Premier Cares Foundation
845.453.1160 or
jgoldfischer@
premiercaresfoundation.org

The Hudson Valley community came out in droves

to support the Premier Care Foundation's first major sponsored event. More than 700 marchers trekked the Walkway Over the Hudson in support of prostate cancer awareness and to help fund free prostate cancer screenings for their neighbors in need of them.

Community businesses supplied refreshments, goods and services while Valleyites of all ages walked the walk in the hope that their efforts would lead to fewer loved ones to miss.

The da Vinci robot was on display for grownups and kids alike. The view on the screen and the precise response of the robotic arms made for a fascinating demonstration. In the hands of Dr. Rahman, HVU's robotics expert, it is a life-saving tool.

Peter Scott, Grand Marshall of the Prostate Walk has a unique insight into prostate cancer awareness and treatment. As Practice Administrator for Hudson Valley Urology, he turned to Dr. Naeem Rahman and the da Vinci robot, with full confidence, when it became clear he needed prostate surgery.

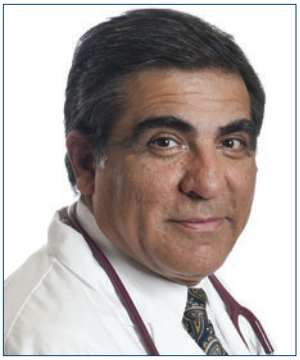
FINALLY, THERE'S A GOOD TREATMENT FOR Fecal Incontinence

In March, 2011, the FDA provided good news for millions of Americans. After reviewing data from years of trials, the agency approved marketing of the InterStim® Therapy System, a surgically implanted device used to help a patient reduce the number of bowel accidents.

It's not something that people like to talk about, even though an estimated 18 million Americans have to deal with it. Fecal incontinence (FI), commonly referred to as "bowel problems," is the inability to hold a bowel movement in until reaching a bathroom. It may also involve accidental leakage of solid or liquid stool.

As of this Spring, however, it's definitely in the interest of people with FI to speak up to their physicians. FDA approval of the InterStim® Therapy System for use in fecal incontinence has finally provided an effective means of controlling, or even stopping, FI in a large proportion of sufferers.

Actual size of the implantable InterStim® device.


Sunil K. Khurana, MD / GI Associates

Gastroenterologists aren't trained in the kind of surgery involved in placing the sacral nerve stimulator. We're fortunate to have a unique infrastructure in place at Premier. When a patient comes in with a problem with bowel incontinence, we evaluate thoroughly to make sure nothing else is going on—be it a tumor, proctitis, or large hemorrhoids—to cause the incontinence. Once we've established that this is the only issue, then we would refer the patient to our colleague Dr. Dan Katz who is skilled in the testing and surgery involved.

"We see a number of patients with fecal incontinence," says Dr. Sunil Khurana of GI Associates, a division of Premier Medical Group. "Most are elderly, but not all, and it is a serious quality of life issue for anyone with the condition. They're afraid to go out to a restaurant or shopping because they don't know when it will happen. Their lives revolve around it."

In the past, there was no good modality to treat fecal incontinence. Physicians prescribed dietary changes, special exercises and bulk agents like Metamucil. Only rarely did these approaches help, but there was little else to offer. "Most of the time," Khurana says, "patients would get resigned to the condition, think of it as a way of life, and stop complaining."

Sacral nerve stimulation has changed the picture. "Now we have something significant to offer our patients," says Khurana. "The studies tell us that, a year after treatment, close to 50 percent of patients have a complete response. Another 30 percent experience a significant diminution in episodes. Being able to help up to 80 percent of patients with the condition is a remarkable achievement."

How it works

The implantable InterStim® system acts like a pacemaker. It delivers mild electrical pulses to the sacral nerves to influence the behavior of the pelvic floor muscles, bowel and anal sphincter. Mandated by the FDA and insurance companies, treatment with sacral nerve stimulation is a two-step process. It begins with a test of whether a patient will be responsive to the stimulation. In a 20-minute office procedure, a thin wire is positioned near the sacral nerves and attached to an exterior power source. If, over a period of two weeks, the patient experiences greater than 50 percent improvement in incontinence episodes, he or she is considered to be a candidate for implantation of the InterStim® device. The temporary wire is replaced with a permanent lead and the stimulator is implanted under the skin on the upper buttock.

"I'm a big proponent of sacral nerve stimulation," says Dr. Dan Katz of Hudson Valley Urology. "I've been using it for years as an adjunct in the treatment of overactive bladder symptoms and have done hundreds of procedures—on patients as old as eighty, as young as 18—with great success.

The procedure is simple, it's easy to do and easy for the patients to tolerate. It's minimally invasive and done under mild sedation, less even than for a colonoscopy.

I've had patients who were going 50 times a day who now are down to 15 times; you can imagine the effect on their lifestyles."


Daniel Katz, MD / Hudson Valley Urology

The beautiful thing about the technique is that it's exactly the same procedure as for urinary incontinence. So some patients will be getting two birds with one stone, treating both conditions with a single procedure.

In my opinion, there is basically no down side to trying. I've done hundreds and hundreds of these and there's never been a major complication. The worst case scenario: if it doesn't work, you're back to where you started. It's a home run if it works and if it doesn't, you're no worse off.

*IN THE TREATMENT OF SYMPTOMATIC BPH**

RAPID RELIEF

THAT KEEPS HIM GOING

*Benign prostatic hyperplasia

RAPAFLO® is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). RAPAFLO® is not indicated for the treatment of hypertension.

Important Safety Information

RAPAFLO® is contraindicated in patients with severe renal impairment (CCr <30 mL/min), severe hepatic impairment (Child-Pugh score ≥10), and with use of strong CYP3A4 inhibitors.

Postural hypotension with or without symptoms (eg, dizziness) may develop when beginning treatment with RAPAFLO®. As with all alpha-blockers, there is a potential for syncope. Patients should be warned of the possible occurrences of such events and should avoid situations where injury could result. RAPAFLO® should be used with caution in patients with moderate renal impairment. Patients should be assessed to rule out the presence of prostate cancer prior to starting treatment with RAPAFLO®. Patients planning cataract surgery should inform their ophthalmologist that they are taking RAPAFLO®.

The most common side effects are retrograde ejaculation, dizziness, diarrhea, orthostatic hypotension, headache, nasopharyngitis, and nasal congestion.

Please see brief summary of Full Prescribing Information on adjacent page.

Models are for illustrative purposes only.

www.rapaflo.com

Watson

RAPAFLO® 8 mg
(silodosin) capsules

READY. SET. GO.

06318 1/10

RAPAFLO®
(silodosin) capsules

BRIEF SUMMARY

For full Prescribing Information, see package insert.

INDICATIONS AND USAGE

RAPAFLO, a selective alpha-1 adrenergic receptor antagonist, is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). RAPAFLO is not indicated for the treatment of hypertension.

CONTRAINDICATIONS

- Severe renal impairment (CCr < 30 mL/min)
- Severe hepatic impairment (Child-Pugh score ≥ 10)
- Concomitant administration with strong Cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ketoconazole, clarithromycin, itraconazole, ritonavir) [*see Drug Interactions*]

WARNINGS AND PRECAUTIONS

Orthostatic Effects

Postural hypotension, with or without symptoms (e.g., dizziness) may develop when beginning RAPAFLO treatment. As with other alpha-blockers, there is potential for syncope. Patients should be cautioned about driving, operating machinery, or performing hazardous tasks when initiating therapy [*see Adverse Reactions and Use in Specific Populations*].

Renal Impairment

In a clinical pharmacology study, plasma concentrations (AUC and C_{max}) of silodosin were approximately three times higher in subjects with moderate renal impairment compared with subjects with normal renal function, while half-lives of silodosin doubled in duration. The dose of RAPAFLO should be reduced to 4 mg in patients with moderate renal impairment. Exercise caution and monitor such patients for adverse events [*see Use in Specific Populations*].

RAPAFLO is contraindicated in patients with severe renal impairment [*see Contraindications*].

Hepatic Impairment

RAPAFLO has not been tested in patients with severe hepatic impairment, and therefore, should not be prescribed to such patients [*see Contraindications and Use in Specific Populations*].

Pharmacokinetic Drug-Drug Interactions

In a drug interaction study, co-administration of a single 8 mg dose of RAPAFLO with 400 mg ketoconazole, a strong CYP3A4 inhibitor, caused a 3.8-fold increase in maximum plasma silodosin concentrations and 3.2-fold increase in silodosin exposure (i.e., AUC). Concomitant use of ketoconazole or other strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin, ritonavir) is therefore contraindicated [*see Drug Interactions*].

Pharmacodynamic Drug-Drug Interactions

The pharmacodynamic interactions between silodosin and other alpha-blockers have not been determined. However, interactions may be expected, and RAPAFLO should not be used in combination with other alpha-blockers [*see Drug Interactions*].

A specific pharmacodynamic interaction study between silodosin and antihypertensive agents has not been performed. However, patients in the Phase 3 clinical studies taking concomitant antihypertensive medications with RAPAFLO did not experience a significant increase in the incidence of syncope, dizziness, or orthostasis. Nevertheless, exercise caution during concomitant use with antihypertensives and monitor patients for possible adverse events [*see Adverse Reactions and Drug Interactions*].

Caution is also advised when alpha-adrenergic blocking agents including RAPAFLO are co-administered with PDE5 inhibitors. Alpha-adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension [*see Drug Interactions*].

Carcinoma of the Prostate

Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently co-exist. Therefore, patients thought to have BPH should be examined prior to starting therapy with RAPAFLO to rule out the presence of carcinoma of the prostate.

Intraoperative Floppy Iris Syndrome

Intraoperative Floppy Iris Syndrome has been observed during cataract surgery in some patients on alpha-1 blockers or previously treated with alpha-1 blockers. This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents; progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs; and potential prolapse of the iris toward the phacoemulsification incisions. Patients planning cataract surgery should be told to inform their ophthalmologist that they are taking RAPAFLO [*see Adverse Reactions*].

Laboratory Test Interactions

No laboratory test interactions were observed during clinical evaluations. Treatment with RAPAFLO for up to 52 weeks had no significant effect on prostate-specific antigen (PSA).

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In U.S. clinical trials, 897 patients with BPH were exposed to 8 mg RAPAFLO daily. This includes 486 patients exposed for 6 months and 168 patients exposed for 1 year. The population was 44 to 87 years of age, and predominantly Caucasian. Of these patients, 42.8% were 65 years of age or older and 10.7% were 75 years of age or older.

In double-blind, placebo controlled, 12-week clinical trials, 466 patients were administered RAPAFLO and 457 patients were administered placebo. At least one treatment-emergent adverse reaction was reported by 55.2% of RAPAFLO treated patients (36.8% for placebo treated). The majority (72.1%) of adverse reactions for the RAPAFLO treated patients (59.8% for placebo treated) were qualified by the investigator as mild. A total of 6.4% of RAPAFLO treated patients (2.2% for placebo treated) discontinued therapy due to an adverse reaction (treatment-emergent), the most common reaction being retrograde ejaculation (2.8%) for RAPAFLO treated patients. Retrograde ejaculation is reversible upon discontinuation of treatment.

Adverse Reactions observed in at least 2% of patients:

The incidence of treatment-emergent adverse reactions listed in the following table were derived from two 12-week, multicenter, double-blind, placebo-controlled clinical studies of RAPAFLO 8 mg daily in BPH patients. Adverse reactions that occurred in at least 2% of patients treated with RAPAFLO and more frequently than with placebo are shown in Table 1.

Table 1 Adverse Reactions Occurring in ≥ 2% of Patients in 12-week, Placebo-Controlled Clinical Trials

Adverse Reactions	RAPAFLO N = 466 n (%)	Placebo N = 457 n (%)
Retrograde Ejaculation	131 (28.1)	4 (0.9)
Dizziness	15 (3.2)	5 (1.1)
Diarrhea	12 (2.6)	6 (1.3)
Orthostatic Hypotension	12 (2.6)	7 (1.5)
Headache	11 (2.4)	4 (0.9)
Nasopharyngitis	11 (2.4)	10 (2.2)
Nasal Congestion	10 (2.1)	1 (0.2)

In the two 12-week, placebo-controlled clinical trials, the following adverse events were reported by between 1% and 2% of patients receiving RAPAFLO and occurred more frequently than with placebo: insomnia, PSA increased, sinusitis, abdominal pain, asthenia, and rhinorrhea. One case of syncope in a patient taking prazosin concomitantly and one case of priapism were reported in the RAPAFLO treatment group.

In a 9-month open-label safety study of RAPAFLO, one case of Intraoperative Floppy Iris Syndrome (IFIS) was reported.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of silodosin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Skin and subcutaneous tissue disorders: *toxic skin eruption, purpura*

Hepatobiliary disorders: *jaundice, impaired hepatic function associated with increased transaminase values*

DRUG INTERACTIONS

Moderate and Strong CYP3A4 Inhibitors

In a clinical metabolic inhibition study, a 3.8-fold increase in silodosin maximum plasma concentrations and 3.2-fold increase in silodosin exposure were observed with concurrent administration of a strong CYP3A4 inhibitor, 400 mg ketoconazole. Use of strong CYP3A4 inhibitors such as itraconazole or ritonavir may cause plasma concentrations of silodosin to increase. Concomitant administration of strong CYP3A4 inhibitors and RAPAFLO is contraindicated [*see Contraindications and Warnings and Precautions*].

The effect of moderate CYP3A4 inhibitors on the pharmacokinetics of silodosin has not been evaluated. Concomitant administration with moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil) may increase concentration of RAPAFLO. Exercise caution and monitor patients for adverse events when co-administering RAPAFLO with moderate CYP3A4 inhibitors.

Strong P-glycoprotein (P-gp) Inhibitors

In vitro studies indicated that silodosin is a P-gp substrate. Ketoconazole, a CYP3A4 inhibitor that also inhibits P-gp, caused significant increase in exposure to silodosin. Inhibition of P-gp may lead to increased silodosin concentration. RAPAFLO is therefore not recommended in patients taking strong P-gp inhibitors such as cyclosporine.

Alpha-Blockers

The pharmacodynamic interactions between silodosin and other alpha-blockers have not been determined. However, interactions may be expected, and RAPAFLO should not be used in combination with other alpha-blockers [*see Warnings and Precautions*].

Digoxin

The effect of co-administration of RAPAFLO and digoxin 0.25 mg/day for 7 days was evaluated in a clinical trial in 16 healthy males, aged 18 to 45 years. Concomitant administration of RAPAFLO and digoxin did not significantly alter the steady state pharmacokinetics of digoxin. No dose adjustment is required.

PDE5 Inhibitors

Co-administration of RAPAFLO with a single dose of 100 mg sildenafil or 20 mg tadalafil was evaluated in a placebo-controlled clinical study that included 24 healthy male subjects, 45 to 78 years of age. Orthostatic vital signs were monitored in the 12-hour period following concomitant dosing. During this period, the total number of positive orthostatic test results was greater in the group receiving RAPAFLO plus a PDE5 inhibitor compared with RAPAFLO alone. No events of symptomatic orthostasis or dizziness were reported in subjects receiving RAPAFLO with a PDE5 inhibitor.

Other Concomitant Drug Therapy

Antihypertensives

The pharmacodynamic interactions between silodosin and antihypertensives have not been rigorously investigated in a clinical study. However, approximately one-third of the patients in clinical studies used concomitant antihypertensive medications with RAPAFLO. The incidence of dizziness and orthostatic hypotension in these patients was higher than in the general silodosin population (4.6% versus 3.8% and 3.4% versus 3.2%, respectively). Exercise caution during concomitant use with antihypertensives and monitor patients for possible adverse events [*see Warnings and Precautions*].

Metabolic Interactions

In vitro data indicate that silodosin does not have the potential to inhibit or induce cytochrome P450 enzyme systems.

Food Interactions

The effect of a moderate fat, moderate calorie meal on silodosin pharmacokinetics was variable and decreased silodosin maximum plasma concentration (C_{max}) by approximately 18 - 43% and exposure (AUC) by 4 - 49% across three different studies. Safety and efficacy clinical trials for RAPAFLO were always conducted in the presence of food intake. Patients should be instructed to take silodosin with a meal to reduce risk of adverse events.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B. RAPAFLO is not indicated for use in women.

An embryo/fetal study in rabbits showed decreased maternal body weight at 200 mg/kg/day (approximately 13-25 times the maximum recommended human exposure or MRHE of silodosin via AUC). No statistically significant teratogenicity was observed at this dose.

Silodosin was not teratogenic when administered to pregnant rats during organogenesis at 1000 mg/kg/day (estimated to be approximately 20 times the MRHE). No maternal or fetal effects were observed at this dose. Rats and rabbits do not produce glucuronidated silodosin, which is present in human serum at approximately 4 times the level of circulating silodosin and which has similar pharmacological activity to silodosin.

No effects on physical or behavioral development of offspring were observed when rats were treated during pregnancy and lactation at up to 300 mg/kg/day.

Pediatric Use

RAPAFLO is not indicated for use in pediatric patients. Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

In double-blind, placebo-controlled, 12-week clinical studies of RAPAFLO, 259 (55.6%) were under 65 years of age, 207 (44.4%) patients were 65 years of age and over, while 60 (12.9%) patients were 75 years of age and over. Orthostatic hypotension was reported in 2.3% of RAPAFLO patients < 65 years of age (1.2% for placebo), 2.9% of RAPAFLO patients ≥ 65 years of age (1.9% for placebo), and 5.0% of patients ≥ 75 years of age (0% for placebo). There were otherwise no significant differences in safety or effectiveness between older and younger patients.

Renal Impairment

The effect of renal impairment on silodosin pharmacokinetics was evaluated in a single dose study of six male patients with moderate renal impairment and seven male subjects with normal renal function. Plasma concentrations of silodosin were approximately three times higher in subjects with moderate renal impairment compared with subjects with normal renal function.

RAPAFLO should be reduced to 4 mg per day in patients with moderate renal impairment. Exercise caution and monitor patients for adverse events.

RAPAFLO has not been studied in patients with severe renal impairment. RAPAFLO is contraindicated in patients with severe renal impairment [*see Contraindications and Warnings and Precautions*].

Hepatic Impairment

In a study comparing nine male patients with moderate hepatic impairment (Child-Pugh scores 7 to 9), to nine healthy male subjects, the single dose pharmacokinetics of silodosin were not significantly altered in patients with hepatic impairment. No dosing adjustment is required in patients with mild or moderate hepatic impairment.

RAPAFLO has not been studied in patients with severe hepatic impairment. RAPAFLO is contraindicated in patients with severe hepatic impairment [*see Contraindications and Warnings and Precautions*].

OVERDOSAGE

RAPAFLO was evaluated at doses of up to 48 mg/day in healthy male subjects. The dose-limiting adverse event was postural hypotension.

Should overdose of RAPAFLO lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by maintaining the patient in the supine position. If this measure is inadequate, administration of intravenous fluid should be considered. If necessary, vasopressors could be used, and renal function should be monitored and supported as needed. Dialysis is unlikely to be of significant benefit since silodosin is highly (97%) protein bound.

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A NEW TECHNIQUE COMES TO THE REGION

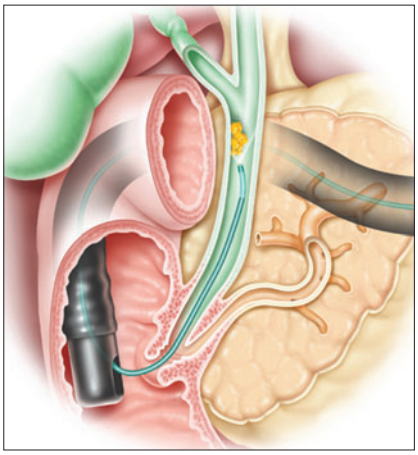
Breaking Up Gallstones

With advanced training on a new endoscopy system and a few tips from a urologist colleague, Dr. Robert Dean performs Vassar Medical Center's first laser lithotripsy on gallstones in the bile duct.

Gallstone disease is a common ailment in the United States, affecting about ten percent of the adult population. In the majority of cases, there are no symptoms and no treatment is needed, but still, close to 800,000 operations are performed each year.

About 15 percent of the people with gallstones will develop stones in the common bile duct, a small tube that carries bile from the gallbladder to the intestines. The obstruction caused by these stones can lead to significant health problems and they almost invariably need to be removed.

Up until the 1970s, this was accomplished through traditional surgery. In 1973, a technique called ERCP (Endoscopic Retrograde Cholangiopancreatography) was introduced and quickly became the gold standard for removing bile duct stones. ERCP combines the use of x-rays and an endoscope. The physician can inject dyes into the bile ducts through the endoscope so the ducts can be clearly seen on x-rays. If the exam shows a gallstone or narrowing of the ducts, guided by the x-ray image the physician can insert instruments into the scope to remove or relieve the obstruction.



An illustration of the SpyGlass Direct Visualization System, with the fiberoptic catheter deployed into the common bile duct.
(courtesy of Boston Scientific Corporation)

"Most of the stones are small stones that we can remove without any fancy stuff," says Dr. Sunil Khurana of GI Associates, a division of Premier Medical Group. "But we also see people who have very large stones, too big to crush and remove with regular ERCP." Until recently, such patients were referred for surgery.

A new tool, the SpyGlass Direct Visualization System, was first made available to gastroenterologists in 2007 and now provides a non-invasive way to deal with these extra large stones. "It's a specialized procedure," says Dr. Khurana. "Because Dr. Robert Dean has developed a special expertise and reputation in dealing with bile duct stones via ERCP, the practice chose him for the advanced training needed to work with the SpyGlass."

Pulverizing stones with SpyGlass + Laser

"The difference with this new technique," explains Dr. Dean, "is that instead of just injecting dye into the bile duct, the SpyGlass has a fiberoptic system you can actually place in the bile duct. And, just as in a colonoscopy, you can see inside with regular, real-time vision of what's going on. That's a significant shift in the paradigm from what we were able to do before."

This visualization of the bile duct allows physicians to perform a range of new procedures, such as taking tissue samples and using laser lithotripsy for gall stones.

"Lithotripsy just means you're breaking up stones," says Dr. Dean. "In the case of such large stones, you have to break them up before they will come out. In ERCP we've had these mechanical devices, wire baskets that could go up into the bile duct and crush the stone. This approach has limitations. First you have to capture the stone, which is difficult just using an x-ray: you're trying to capture a 3-dimensional thing using a 2-dimensional visualization.With the SpyGlass, we can put the catheter into the bile duct and actually visualize the stone itself, instead of just seeing a negative image of it. And since we can see the stone, we can point a laser at the stone and pulverize it.

Robert S. Dean, MD

"The laser I am using for the bile duct is a tool that has been used by urologists for years on stones in the urinary system. So when I started to employ this technique for the bile duct, in order to become familiar with the laser itself, I worked with Dr. Mark Libin of Hudson Valley Urology to understand his technique.

Before using it, you have to understand the safety characteristics of the laser. You can, for example, set the wave-length and the frequency of the pulse to ensure that the laser will affect only the stone and diminish the risk to actual tissue. Stones in the bile duct are very different in composition than stones in the urinary tract. We've found that the stones in the bile duct respond better to a longer wave-length and less frequent pulsation than urinary stones. We're still tinkering a little with the setting, and just getting better and better."

AFTER A THIRTY YEAR CAREER IN MEDICINE...

So Long, Dr. Sotolongo

Dr. José Sotolongo began his medical practice in 1984, after completing a 4-year residency and a fellowship in neurourology. He worked in private practice and as a full-time academic at Mount Sinai until 1992, when he moved to the Hudson Valley and joined Hudson Valley Urolology.

Premier Health magazine caught up with him on August 31, his last day before retirement, and asked him to look back on his career.

PH: Dr. Sotolongo, what do you consider to be the most significant developments you've seen in urology over the course of your thirty-year career?

JS: I would say the most remarkable development I've seen in all these years has been the use of endoscopy, meaning fiberoptic instruments that allow us to inspect the interior of the urinary tract without cutting somebody. When I started training in 1980 we were cutting people open to remove kidney stones and bladder stones. Very soon thereafter, as early as `84-`85, that started falling away as we saw more and better fiber optic instruments that we could use to access stones without cutting people. That was, I think, a revolutionary development in urology.

More recently, the use of robotic surgery is something that has begun to revolutionize the practice of urology as well. It has not had its full impact yet, I don't think.

What single piece of advice would you give to a young physician starting out today?

The most important thing I've found, something that's helped me is: Be true to your own principles, true to what you went into medicine for. That's advice for any physician, not just urologists. Don't let anything persuade you to take any shortcuts. Just do what you think is best for your patients and stick to your guns.

Is there some information that you've found yourself repeatedly giving to patients?

The best piece of advice you can give a patient is to be mindful of and respect your body in terms of what you consume. People eat the wrong things in the wrong volume. And that has impact on things like forming kidney stones, in my field, diabetes, and hypertension. Be very careful of what you put into your body.

Are then any aspects of being a practicing physician that you expect to miss?

I expect I will really miss the interaction with my patients. They have been, over all, very grateful and very expressive of that gratitude and very forthcoming about their feelings. Sometimes it crosses into a sort of friendship, a very congenial relationship that develops when you've had a patient for years. I think I will miss that a great deal.

And I will miss the interaction with my colleagues. I've enjoyed tremendously working with many physicians in this practice and other specialties who have been supportive and congenial and just wonderful to work with.

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- In a maintenance trial, of the patients who achieved clinical response at week 4, greater proportions of HUMIRA-treated patients, compared to placebo patients, were in clinical remission at week 26 (40% vs 17%, *P*<0.001) and week 56 (36% vs 12%, *P*<0.001)[1]
- HUMIRA can be self-injected at home or almost anywhere, after a physician determines that it is appropriate and after proper training in injection technique. Instruct patients to refer to storage instructions found in the Medication Guide[1]

Indications[1]

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Safety Considerations[1]

Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. These infections include active tuberculosis (TB), reactivation of latent TB, invasive fungal infections, and bacterial, viral, and other infections due to opportunistic pathogens. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Malignancies

Lymphoma, including a rare type of T-cell lymphoma, and other malignancies, some fatal, have been reported in patients treated with TNF blockers, including HUMIRA.

Other Serious Adverse Reactions

Patients treated with HUMIRA also may be at risk for other serious adverse reactions, including anaphylaxis, hepatitis B virus reactivation, demyelinating disease, cytopenias, pancytopenia, heart failure, and a lupus-like syndrome.

HUMIRA®
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IMPORTANT SAFETY INFORMATION[1]

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

HUMIRA should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before HUMIRA use and during therapy. Treatment for latent TB should be initiated prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

The risks and benefits of treatment with HUMIRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

- Do not start HUMIRA in patients with an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- Exercise caution in patients with chronic or recurrent infection or with underlying conditions which may predispose them to infection, patients who have been exposed to TB, patients with a history of opportunistic infection, or patients who have resided or traveled in regions where TB or mycoses are endemic.
- Patients who develop a new infection should undergo a prompt and complete diagnostic workup, and appropriate antimicrobial therapy should be initiated.
- Drug interactions with biologic products: Concurrent use of anakinra or abatacept with HUMIRA is not recommended, as the combination of anakinra or abatacept with TNF blockers has been associated with an increased risk of serious infections. This risk has also been observed with rheumatoid arthritis patients treated with rituximab who received subsequent treatment with a TNF blocker.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which HUMIRA is a member. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases has occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

- The risks and benefits of HUMIRA treatment should be considered prior to initiating or continuing therapy in a patient with known malignancy.
- More cases of malignancies were observed among HUMIRA-treated patients compared to control patients in clinical trials.
- Non-melanoma skin cancer (NMSC) has been reported during clinical trials for HUMIRA-treated patients. All patients, particularly those with history of prolonged immunosuppressant or PUVA therapy, should be examined for the presence of NMSC prior to and during treatment with HUMIRA.
- In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.
- Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use.
- Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

HYPERSENSITIVITY

- Anaphylaxis and angioneurotic edema have been reported rarely following HUMIRA administration.
- If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.

HEPATITIS B VIRUS REACTIVATION

- Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.
- Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy.
- Exercise caution in patients who are carriers of HBV and monitor them during and after treatment with HUMIRA.
- Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation.
- Exercise caution when considering resumption of HUMIRA therapy after appropriate treatment for HBV.

NEUROLOGIC REACTIONS

- TNF blockers, including HUMIRA, have been associated in rare cases with new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis and Guillain-Barré syndrome.
- Exercise caution when considering HUMIRA for patients with these disorders.

HEMATOLOGIC REACTIONS

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia (e.g. thrombocytopenia, leukopenia) has been infrequently reported with HUMIRA.
- Consider stopping HUMIRA in patients with significant hematologic abnormalities.

CONGESTIVE HEART FAILURE

- Worsening or new onset congestive heart failure (CHF) may occur.
- Exercise caution in patients with CHF and monitor them carefully.

AUTOIMMUNITY

- Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome.
- Discontinue treatment if symptoms of a lupus-like syndrome develop.

IMMUNIZATIONS

- Patients on HUMIRA should not receive live vaccines.
- It is recommended that juvenile idiopathic arthritis patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy.

ADVERSE REACTIONS

- The most common adverse reactions in HUMIRA clinical trials (incidence >10%) were: infections (e.g. upper respiratory, sinusitis), injection site reactions, headache, and rash.

Please see Brief Summary of full Prescribing Information on following pages.

Reference: 1. HUMIRA Injection [package insert]. North Chicago, IL: Abbott Laboratories.

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PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNINGS: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

HUMIRA should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before HUMIRA use and during therapy. Treatment for latent TB should be initiated prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

The risks and benefits of treatment with HUMIRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy. *[See Warnings and Precautions and Adverse Reactions]*

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which HUMIRA is a member. *[See Warnings and Precautions]*

Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases has occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

INDICATIONS AND USAGE

Rheumatoid Arthritis HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

Juvenile Idiopathic Arthritis HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 4 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

Psoriatic Arthritis HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

Ankylosing Spondylitis HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Crohn's Disease HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Plaque Psoriasis HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warnings and Warnings and Precautions]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS (see also Boxed WARNINGS)

Serious Infections Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease. The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions and Drug Interactions]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy.

Anti-tuberculosis therapy should also be considered prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Tuberculosis should be strongly considered in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

HUMIRA should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with HUMIRA should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

Invasive Fungal Infections For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

Malignancies The risks and benefits of TNF-blocker treatment including HUMIRA should be considered prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 32 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), and plaque psoriasis (Ps), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.6 (0.38, 0.93) per 100 patient-years among 6694 HUMIRA-treated patients versus a rate of 0.5 (0.28, 1.05) per 100 patient-years among 3749 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 45 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD and Ps, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer During the controlled portions of 32 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, and Ps, the rate (95% confidence interval) of NMSC was 0.7 (0.50, 1.11) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.06, 0.56) per 100 patient-years among control-treated patients. All patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment should be examined for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF blocker-treated patients compared to control-treated patients. In the controlled portions of 32 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, and Ps, 3 lymphomas occurred among 6694 HUMIRA-treated patients versus 1 among 3749 control-treated patients. In 45 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD and Ps with a median duration of approximately 0.6 years, including 22,026 patients and over 32,000 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1] Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases has occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

Hypersensitivity Reactions In postmarketing experience, anaphylaxis and angioneurotic edema have been reported rarely following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, administration of HUMIRA should be discontinued immediately and appropriate therapy instituted. In clinical trials of HUMIRA in adults, allergic reactions overall (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients.

Hepatitis B Virus Reactivation Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. In patients who develop HBV reactivation, HUMIRA should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known.

Neurologic Reactions Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS), and peripheral demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders.

Hematological Reactions Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Discontinuation of HUMIRA therapy should be considered in patients with confirmed significant hematologic abnormalities.

Use with Anakinra Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions]*.

Heart Failure Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. Physicians should exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Autoimmunity Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, treatment should be discontinued *[see Adverse Reactions]*.

Immunizations In a placebo-controlled clinical trial of patients with rheumatoid arthritis, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

It is recommended that juvenile idiopathic arthritis patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

Use with Abatacept In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions]*.

ADVERSE REACTIONS

Clinical Studies Experience The most serious adverse reactions were:

- Serious Infections *[see Warnings and Precautions]*
- Malignancies *[see Warnings and Precautions]*

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of Studies RA-I, RA-II, RA-III and RA-IV was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections In the controlled portions of the 32 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD and Ps, the rate of serious infections was 4.7 per 100 patient-years in 6694 HUMIRA-treated patients versus a rate of 2.7 per 100 patient-years in 3749 control-treated patients. Serious

infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions]*.

Tuberculosis and Opportunistic Infections In 45 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD and Ps that included 22,026 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.22 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. In a subgroup of 8940 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.07 per 100 patient-years and the rate of positive PPD conversion was 0.06 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.07 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions]*.

Autoantibodies In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in patients with Crohn's disease with control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with plaque psoriasis with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients.

Immunogenicity Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult rheumatoid arthritis patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with juvenile idiopathic arthritis, adalimumab antibodies were identified in 16% of HUMIRA-treated patients. In patients receiving concomitant methotrexate, the incidence was 6% compared to 26% with HUMIRA monotherapy.

In patients with ankylosing spondylitis, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with rheumatoid arthritis. In patients with psoriatic arthritis, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with rheumatoid arthritis; however, in patients receiving concomitant methotrexate the rate was 7% compared to 1% in rheumatoid arthritis. In patients with Crohn's disease, the rate of antibody development was 3%. In patients with plaque psoriasis, the rate of antibody development with HUMIRA monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 ug/ml. Among the patients whose serum adalimumab levels were < 2 ug/ml (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In plaque psoriasis patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

Other Adverse Reactions The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week. Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Rheumatoid Arthritis Studies

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
	(N=705)	(N=690)
Adverse Reaction (Preferred Term)		
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%

(continued)

Table 1. *continued*

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
	(N=705)	(N=690)
Laboratory Tests*		
Laboratory test abnormal	8%	7%
Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%

* Laboratory test abnormalities were reported as adverse reactions in European trials

** Does not include injection site erythema, itching, hemorrhage, pain or swelling

Juvenile Idiopathic Arthritis Clinical Studies In general, the adverse reactions in the HUMIRA-treated pediatric patients in the juvenile idiopathic arthritis (JIA) trial were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions, Adverse Reactions]*. Important findings and differences from adults are discussed in the following paragraphs.

HUMIRA was studied in 171 pediatric patients, 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

A total of 45% of children experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in children receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

In the first 48 weeks of treatment, non-serious hypersensitivity reactions were seen in approximately 6% of children and included primarily localized allergic hypersensitivity reactions and allergic rash.

Isolated mild to moderate elevations of liver aminotransferases (ALT more common than AST) were observed in children with JIA exposed to HUMIRA alone; liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment.

In the JIA trial, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of children treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK). Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Crohn's Disease Clinical Studies HUMIRA has been studied in 1478 patients with Crohn's disease in four placebo-controlled and two open-label extension studies. The safety profile for patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies HUMIRA has been studied in 1696 patients with plaque psoriasis in placebo-controlled and open-label extension studies. The safety profile for patients with plaque psoriasis treated with HUMIRA was similar to the safety profile seen in patients with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in plaque psoriasis patients, HUMIRA-treated patients had a higher incidence of arthralgia when compared to controls (3% vs. 1%).

Postmarketing Experience Adverse reactions have been reported during post-approval use of HUMIRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar)

Vascular disorders: Systemic vasculitis

DRUG INTERACTIONS

Methotrexate Although methotrexate (MTX) reduces the apparent adalimumab clearance, the data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Biologic Products In clinical studies in patients with RA, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions]*. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information to provide recommendations regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, Crohn's Disease, and plaque psoriasis.

Live Vaccines

Live vaccines should not be given concurrently with HUMIRA *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category B - There are no adequate and well-controlled studies in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, HUMIRA should be used during pregnancy only if clearly needed.

Pregnancy Registry: To monitor outcomes of pregnant women exposed to HUMIRA, a pregnancy registry has been established. Physicians are encouraged to register patients by calling 1-877-311-8972.

Nursing Mothers It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from HUMIRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use Safety and efficacy of HUMIRA in pediatric patients for uses other than juvenile idiopathic arthritis (JIA) have not been established.

Juvenile Idiopathic Arthritis In the JIA trial, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age. HUMIRA has not been studied in children less than 4 years of age, and there are limited data on HUMIRA treatment in children with weight <15 kg. The safety of HUMIRA in pediatric patients in the JIA trial was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions]*.

Post-marketing cases of malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Warnings and Precautions]*.

Geriatric Use A total of 519 rheumatoid arthritis patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these subjects and younger subjects. The frequency of serious infection and malignancy among HUMIRA treated subjects over 65 years of age was higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of HUMIRA were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.

PATIENT COUNSELING INFORMATION

Patients or their caregivers should be provided the HUMIRA "Medication Guide" and provided an opportunity to read it and ask questions prior to initiation of therapy. The healthcare provider should ask the patient questions to determine any risk factors for treatment. Patients developing signs and symptoms of infection should seek medical evaluation immediately.

Patient Counseling Patients should be advised of the potential benefits and risks of HUMIRA. Physicians should instruct their patients to read the Medication Guide before starting HUMIRA therapy and to reread each time the prescription is renewed.

- **Infections**
  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.
- **Malignancies**
  Patients should be counseled about the risk of malignancies while receiving HUMIRA.
- **Allergic Reactions**
  Patients should be advised to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the prefilled syringe contains latex.
- **Other Medical Conditions**
  Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

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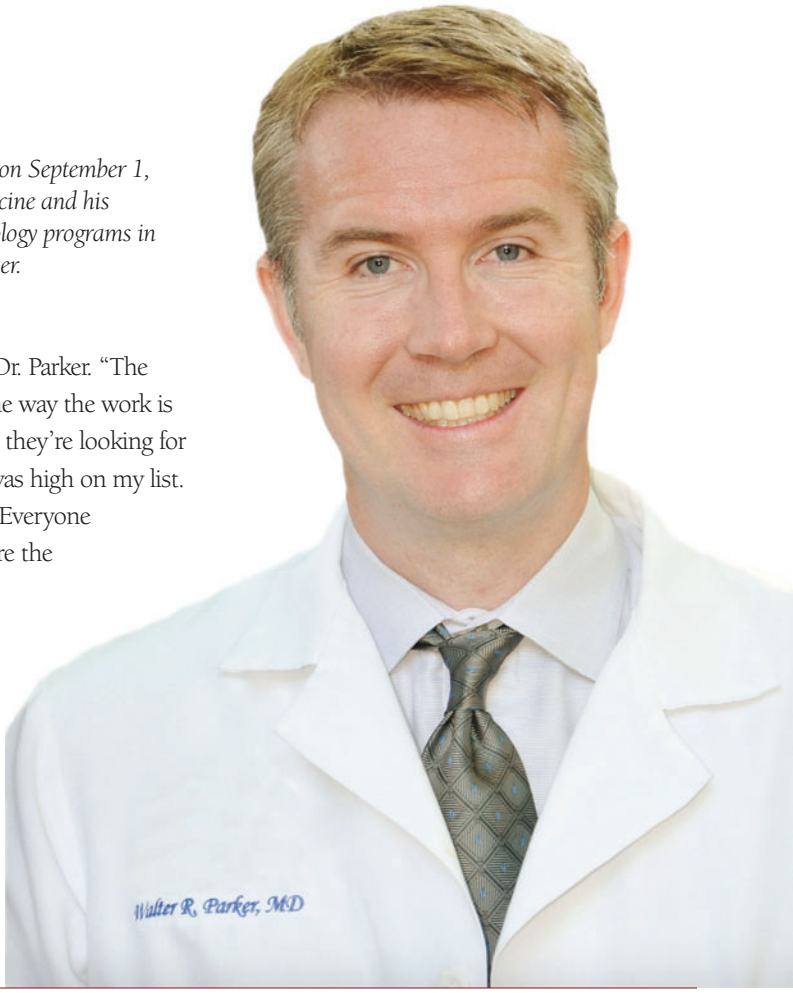
Welcome, Dr. Parker

Walter R. Parker, MD
Hudson Valley Urology

Dr. Parker joined the Hudson Valley Urology division of Premier Medical Group on September 1, 2011. With his excellent education at the University of Rochester School of Medicine and his training at the University of Michigan Department of Urology, one of the top urology programs in the nation, "the practice is lucky to have attracted him," says Dr. Evan Goldfischer.



"You consider many things when you're looking for a position," says Dr. Parker. "The quality of the group's management becomes very important, and the way the work is divvied out. Then you're trying to find a good match between what they're looking for from you and what you want to do. Finding a well-run, equitable practice was high on my list.

"Over the course of my interviews I've met most of the doctors at HVU. Everyone seems very willing to work with me. The practice model is really making sure the patient is getting good care and that everybody's providing what they can provide best and doing what they're interested in doing.

"I'm looking forward to finding out how I will fit in. I think I come with a very broad training background. I imagine in the years to come I will develop my own niche, yet at the beginning I will undoubtedly do a lot of general urology. HVU will be able to take advantage of some of the experience I have, such as in urethral reconstruction techniques and robotic surgery. I certainly would be very happy to take on some of the workload."