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Health & Science

Coming Next Week

Southeast struggles with sky-high STDs

While most of the country is talking about eradicating syphilis, high STD rates in the Southeast are exacerbated by poverty, geography, conservatism and lack of resources.

Bone marrow transplants tapped for "bold new step" in disease treatment

AT A GLANCE

Broadening the applications of BMT include treating autoimmune disease, but scientific questions about the expensive experimental procedure abound.

Mark Moran

AMNEWS STAFF

A 9-YEAR-OLD OREGON GIRL WAS scheduled this month to receive a bone marrow transplant for severe juvenile rheumatoid arthritis.

The procedure, which appears to be unprecedented in the United States for this condition, would make Mollie Hauck, of Canby, Ore., a pioneer in the use of BMT to treat autoimmune disease.

Physicians at Oregon Health Sciences University's Doernbecher Children's Hospital in Portland planned to remove bone marrow stem cells, ablate her immune system with chemotherapy, then re-infuse the stem cells with the hope that they will regenerate a healthy immune system.

BMT for autoimmune disease is a nascent but expanding area of experi-

mental therapy that, if proven successful, could change the way physicians think about rheumatoid arthritis, multiple sclerosis, lupus and scleroderma: from chronic illnesses requiring long-term palliative care, to conditions that may be all but cured by rejuvenating a defective immune system.

Yet a host of scientific questions are yet to be answered, and the real world applications of a procedure that can cost upward of \$100,000 remain to be seen.

"This is a bold new step in the treatment of these diseases, but the

jury is still out," said David Sherry, MD, director of pediatric rheumatology at Children's Hospital and Regional Medical Center in Seattle. Dr. Sherry, who is Mollie's rheumatologist, emphasized that her condition is of the severest sort and that the transplant follows years of expensive and painful standard care.

"Where this is going to settle down in our armamentarium is yet to be revealed," he said. "If we refine our techniques over the next 10 years so [the procedure] becomes safer and proves to be curative, it may be used

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for milder disease."

Prevalence figures for autoim-

mune disorders vary due to differences in diagnostic criteria, but one analysis of prevalence and incidence studies using conservative criteria. published in Clinical Immunology and Immunopathology (September 1997), found more than 8 million people with one of 24 autoimmune diseases: 154,278 with multiple sclerosis; 1,736,099 with rheumatoid arthritis: 63,052 with systemic lupus erythe-

matosus; and 8,922 with scleroderma. Yet physicians agree that BMT. which has had an 8%-9% mortality rate in Europe, should only be considered for very ill patients who haven't responded to conventional therapy. Spokespersons for the American Autoimmune Related Diseases Assn. and the National Multiple Sclerosis Society said BMT isn't recommended for the vast majority of patients.

Still, optimism about BMT for autoimmune disease is high, based on animal research and successful human trials in Europe. At least two research consortia — one centered at the Fred Hutchinson Cancer Research Center in Seattle and another

at Northwestern University Medical School in Chicago — have developed protocols for performing bone marrow transplants on patients with severe autoimmune disease.

Approximately 48 BMTs have been performed in the United States for MS, lupus, scleroderma and rheumatoid arthritis. More than 200 of the operations have been performed in Europe, where the mortality was 8% to 9%.

The National Institute of Allergy and Infectious Diseases has issued requests for proposals to conduct clinical trials to test the procedure and is negotiating contracts with research groups.

Broadening applications

THE BROADENING APPLICATION OF bone marrow transplant has been furthered by a host of advances making the procedure safer and more efficient. These include use of "committed" stem cells, drugs that allow stem cells to rapidly regenerate, and better surveillance and treatment of infection.

Last month, physicians at Massachusetts General Hospital reported

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the successful use of BMT to induce tolerance to a kidney graft. The principle of using BMT to establish tolerance for organ grafts has been established in animal research and in clinical cases in which renal transplants were performed many years after previous bone marrow transplantation. In those instances, tolerance was induced by the previous bone marrow transplant without long-term immunosuppressive therapy.

But the MGH patient is believed to be the first to receive a dual transplant for the deliberate purpose of in-

ducing tolerance. The patient, who developed kidney failure as a result of underlying multiple myeloma, received a kidney transplant and a BMT from her sister in September 1998. Use of the drug cyclosporin was discontinued after 73 days, and the patient has maintained tolerance since then.

Meanwhile, the notion that chronically debilitating conditions might be cured by BMT runs counter to orthodox thinking The methodological hurdles to assessing the procedure are not small

"It's difficult to dissect out the ef-

"This is a bold new step in the treatment of these diseases, but the jury is still out."

David Sherry, MD, Children's Hospital and Regional Medical Center in Seattle

fects of chemotherapy and the trans plant, and it will take at least two to three years of following a reasonable number of patients to see if their performance is better than what we might have expected naturally," said MS expert Jerry Wolin sky. MD, professor of neurology at the University of Texas, Houston. Health Science Center

In the case of MS, for which there is the most extensive BMT experience, the role of immune

dysfunction in the disease is debated. It is still an open question whether the disease is a primary autoimmune disease." Dr. Wolinsky said.

Among physicians who have registered caution about the procedure is one who was among the first to perform it in the United States. Richard Burt, MD, director of allogenic stem cell transplantation at Northwestern University Memorial Hospital, said the mechanism by which autoimmune diseases appear to remit following BMT is unknown. The notion that stem cells can regenerate into a healthy immune system is unproven and may not account wholly for apparent successes.

Some of the reported success stories may be due to "expectation bias" on the part of physicians and patients. "The more risky a procedure is the more expectation bias on the part

of people who do it," he said.

As has happened with BMT for breast cancer, the procedure is liable to be attractive to desperately ill patients seeking a last resort. For this reason. Dr. Burt and others involved in the research emphasize that the procedure should be performed at qualified transplant centers under protocols.

In multicenter trials of BMT for MS, lupus and rheumatoid arthritis, Dr Burt and colleagues hope to use "gene marking" to understand the mechanism by which transplanted patients remit or relapse. By inserting a marker into transplanted stem cells, it may be possible to determine if regenerated cells, or surviving host immune cells, are associated with relapse

Dr. Burt said he also hopes to study the cost-effectiveness of the procedure by gathering data on past medical costs incurred by patients receiving standard care. At Northwestern, 10 patients with MS, seven with lupus and four with rheumatoid arthritis have received BMT. Of those, about a third were paid for by insurance, the others were free or paid for out-ofpocket by families.

Dr. Burt agreed that the procedure is causing a paradigm shift. When he began pioneering BMT for autoim mune disease 11 years ago, he met "a stiff wall of resistance," from the medical community.

"Now the pendulum has swung." he said. "The truth is probably some where in the middle. It could be an effective treatment for some autoimmune disease but not for others where the risk may be too high. What we've seen is a shift in the medical community from thinking (about autoimmune disease] in terms of palliative care and doing no harm, to taking a risk that you might do some harm in order to potentially cure." •



INDICATIONS AND USAGE

FLOMAX* is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH): FLOMAX* is not indicated for the treatment of hypertension. CONTRAINDICATIONS

FLOMAX* as contraindicated in patients known to be hypersensitive to tamsulosin or any component of FLOMAX*

The signs and symptoms of orthostasis (postural hypotension, dizziness and vertigo were detected more frequently in FLOMAX*-treated patients than in placebo recipients. As with other alpha-adrenergic blocking agents, there is a potential risk of syncope (see ADVERSE REACTIONS).

Patients beginning treatment with FLOMAX* should be cautioned to avoid situations where injury could result should syncope occur.

PRECAUTIONS

General

General

I Carcinomia of the prostate. Carcinoma of the prostate and BPH cause many of the same hymptoms. These two diseases frequently occass? Patients should be availuated prior to the start of FLOMAX* therapy to rule out the presence of carcinoma of the prostate.

2) Drug-Drug Interactions: The pharmacokinetic and pharmacodynamic interactions between FLOMAX* and other alpha-adrenency blocking agents have not been determined. However, interactions may be expected and FLOMAX* should NOT be used in combination with other alpha-adrenency blocking agents.

The pharmacokinetic interactions between cinebidine and FLOMAX* was investigated. The results indicate significant changes in tempulosin clearance (26% decrease) and AUC (44% increase). Therefore, FLOMAX* should be used with caution in combination with other alpha-adrenency and the particularly at dosies higher than 0.4 mg.

particularly at dosies higher than 0.4 mg.

Results from limited in vitro and in vivo drug-drug interaction studies between temporomiant.

Results from limited in vitro and in vivo drug-drug interaction studies between tamsulosin and warfarin are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and FLOMAX.

Information for Patients (see Patient Package Insert)

Patients should be told about the possible occurrence of symptoms related to postural hypotension such as dizziness when taking FLOMAX* and they should be cautioned about driving, operating machinery or performing hazardous tasks.

Patients should be advised not to crush, chew or open the capsules of FLOMAX

No laboratory test interactions with FLOMAX" are known. Treatment with FLOMAX" for up to 12 months had no significant effect on prostate-specific antigen (PSA)

Pregnancy Teratogenic Effects, Pregnancy Category B. Administration of tamisulosin to pregnant ternale rats at dose levels up to 300 mg/kg/day (approximately 50 times the human therapeutic ALIC exposure) revealed no evidence of harm to the fetus. Administration of tamisulosin to pregnant rabbds at dose levels up to 50 mg/kg/day produced no evidence of letal harm. FLOMAX* is not indicated for use in women.

Nursing Mothers FLOMAX* is not indicated for use in women

Pediatric Use FLOMAX* is not indicated for use in pediatric populations.

Carcinogenesis, Mutagenesis, and Impairment of Fertility Rats administered doses up to 43 mg/kg/day in males and 52 mg/kg/day in temales had no increases in tumor incidence, with the exception of a modest increase in the frequency of mammary gland fibroadenomas in temale rats receiving doses 2.5.4 mg/kg (Pc. 0.015). The highest doses of tamsulosin evaluated in the rat carcinogenicity study produced systemic exposures (AUC) in rats 3 times the exposures in men receiving the maximum therapeutic dose of 18 mg/kg.

Mice were administered doses up to 127 mg/kg/day in males and 158 mg/kg/day in temales. There were no significant tumor findings in male mice. Female mice treated for 2 years with the two highest doses of 45 and 158 mg/kg/day had statistically significant increases in the two highest doses of 45 and 158 mg/kg/day had statistically significant increases in the incidence of mammary gland fibroadenomas (P< 0.0075) and adenocarcinomas (P< 0.0075). The highest dose levels of tamsulosis evaluated in the mice carcinogenicity study produced the highest dose levels of tamsulosis evaluated in the mice carcinogenicity study produced systemic exposures (AUC) in mice 8 times the exposures in men receiving the maximum therapeutic dose of 0.8 mg/day.

The increased incidences of mammary gland neoplasms in female rats and mice were considered secondary to tamsulosin-induced hyperprolactinemia. It is not known if FLOMAX* elevates protectin in humans. The relevance for human risk of the findings of profactin-mediated endocrine tumors in rodents is not known.

Tamsulosin produced no evidence of mutagenic potential in vitro in the Ames reverse mutation test, mouse hymphoma thymidine kinase assay, unscheduled DNA repair synthesis assay, and chromosomal aberration assays in chinese hamster ovary cells or human lymphocytes. There were no mutagenic effects in the in vivo sister chromatid exchange and mouse micromicleus assay.

Studies in rata revealed significantly reduced tertility in males dosed with single or multiple daily doses of 300 mg/kg/day of tamsulosin (AUC exposure in rata about 50 times the daily doses of 300 mg/kg/day of tamsulosin (AUC exposure in rata about 50 times the human exposure with the maximum therapeutic dose). The mechanism of decreased human exposure with the maximum therapeutic dose). The mechanism of signal plug tertility in male rats is considered to be an effect of the compound on the viginal plug tertility in male successful dose of changes of semen content or impairment of ejaculation. The formation, possibly due to changes of semen content or impairment of ejaculation. The formation, possibly due to changes of semen compound by 3 days after a single dose and effects on famility in males were completely reversed within 4 weeks after multiple dosing. Effects or famility in males were completely reversed within 4 weeks of discontinuation of multiple dosing. Multiple doses of 10 and 100 mg/kg/day nine weeks of discontinuation of multiple dosing. Multiple doses of 10 and 100 mg/kg/day nine weeks of discontinuation of multiple dosing. Multiple doses of 10 and 100 mg/kg/day nine weeks of discontinuation of multiple dosing. Multiple doses of 10 and 100 mg/kg/day nine weeks of discontinuation of multiple dosing. Multiple doses of 10 and 100 mg/kg/day nine weeks of discontinuation of multiple dosing male rats. Effects of tamsulosin on sperm counts or sperm function have not been evaluated.

Studies in termile rats revealed significant reductions in tertility after single or multiple dosing with 300 mg/kg/day of the R-Isomer or racemic mixture of termilation, respectively dosing with 300 mg/kg/day of the R-Isomer or racemic mixture at the reductions in tertility after single doses were considered to be associated with imparments in tertilization. Multiple dosing with 10 or 100 mg/kg/day of the racemic mixture did not significantly after tertility in temple rats.

ADVERSE REACTIONS The incidence of treatment emergiant adverse events has been ascertained from six short-term U.S. and European placebo-controlled clinical triats in which daily doses of 0.1 to 0.8 mp FLOMAX* were used. These sludies evaluated safety in 1783 patients treated with FLOMAX* and 798 patients administered placebo Table 3 sum marzes the treatment emergent adverse events that occurred in 2.2% of patients receiving marzes the treatment emergent adverse events that occurred in 2.2% of patients receiving marzes the treatment emergent adverse events that occurred in 2.2% of patients receiving the placebo group, during two 13-week U.S. trials (US92-03A and US93-01) conducted in 1487 men.

TABLE 3 THE ATMENT EMERGENT! ADVERSE EVENTS OCCURRING IN 2% OF FLOMAX OR PLACEBO PATIENTS IN TWO U.S. SHORT-TERM PLACEBO CONTROLLED

BOOY SYSTEM ADVERSE EVENT	PEOMAST CHCUPS		PLACEBO:
	0 4 mg h-200	1.8 mg	n=402
BODY AS WHOLE:		(Constation of Co.	Suppression and
Headache	97.(19.0%)	104 (21 75)	99 (20 1%)
Infection:	45 (9.0%)	43 (10 8%)	37 (7 5%)
Anthenia -	39-17-8%	42 16 5%1	27 (\$ 654)
Back Plyst.	36 (7.0%)	41 (8.3%)	97 (8.5%)
Chest Paill	20144-0%	20 (4.1%)	(0.0.7%)
NERWOUS SYSTEM			
Dizpriess.	75 (14.9%)	(04)17.5%	50 (10 1%)
Somnolericie .	15 (3:0%)	21 (4 3%)	0 (1 (0%)
Insomna	12 (2:4%)	(3.4%)	310 676
Libido Decreased	9-(1.0%)	10 (2 0%)	6.(1.8%)
RESPIRATORY SYSTEM			The second second
Ehroba-	66 (12.1%)	08 (17 9%)	47.08.251
Phoryrights	25 (5.8%)	25.15,1%	22 (4.7%)
Cough increased -	17.13-4%)	22 [4 5%]	(2 (2 4%)
Smidte	11 (2.2%)	78 (0.7%)	# 1, 4zer
DIGESTIVE SYSTEM		0.000000	in land
Diarrivos	31 16 2 201	21.64.354	22 (4.5%)
Nausee -	12 (2.6%)	19 /3 9%	V (1.4%)
Tooth Disortter	0.01250	1015 045	11.00
UROGENITAL SYSTEM		66 (10 th))	1 (1.2%)
Abrema Casulatin	42 (0.45)	MR 1 (N. 1762)	110 8 41
SPECIMI SENSES	1020	10 (2:0%)	0.00450
Ambiyopis	10.24		
			are and deep building and the

The adverse event was present prior to or at the time of initial dosing with double blind shudy medication, disappeared completely, and then reappeared during double-blind treatment.

The adverse event was present prior to or at the time of initial dosing with double blind study medication, disappeared completely, and then reappeared during double-blind treatment. Signs and Symptoms of Orthostasis in the two U.S. studies, symptomistic postural hypotension was recorded by 0.2% of patients (1 of 502) in the 0.4-mg group, 0.4% of patients (2 of 492) in the 0.8-mg group, and by ne patients in the placebo group. Syncope was reported by 0.2% of patients (3 of 493) in the placebo group. Describes was reported by 15% of patients (3 of 493) in the placebo group. Describes was reported by 15% of patients (25 of 502) in the 0.4-mg group in the 0.8-mg group received 0.4-mg once daily the posterior of patients (8 of 253) who received placebo. At 8 hours 0.4-mg once daily and in 3% of the patients (8 of 253) who received placebo. At 8 hours 0.4-mg once daily and in 3% of the patients (8 of 253) who received placebo. (Note who received FLOMAX* 0.4-mg once daily for the list was observed in the 18-mg once daily group and 5.4 of the 502 patients (15%) in the FLOMAX* 0.8-mg once daily group and 5.4 of the 502 patients (15%) in the FLOMAX* 0.8-mg

493 patients (11%) in the placebo group.

Because orthostasis was detected more frequently in FLOMAX*-treated patients than in placebo recipients, there is a potential risk of syncope isses WARNINGS*).

Abnormal Ejaculation Abnorma: ejaculation includes ejaculation fature, ejaculation disorder, retrograde ejaculation and ejaculation decrease. As shown in Table 3, abnormal ejaculation was associated with FLOMAX* administration and was dose-related in the U.S. studies. Withdrawal from these clinical studies of FLOMAX* because of abnormal ejaculation was also dose-dependent with 8 of 492 patients (1.6%) in the 0.8-mg group, and no patients in the 0.4-mg or placebo groups, discontinuing treatment due to abnormal ejaculation.

OVERDOSAGE Should overdosage of FLOMAX* lead to hypotension (See WARNINGS and ADVERSE REACTIONS), support of the cardiovascular system is of liest importance. Restoration of blood pressure and normalization of hear rate may be accomplished by keeping the patient in the supring position. If this measure is inadequate, then administration of intravenous had be considered. If necessary, vasopressors should their be used and renal function should be monitored and supported as needed. Laboratory data indicate that tambulosin is 94% to 99% protein bound; therefore, dialysis in unlikely to be of benefit.

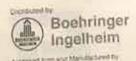
One patient reported an overdose of thirty 0.4-mg capsules of FLOMAX*. Following the ingestion of the capsules, the patient reported a severe headache.

DOSAGE AND ADMINISTRATION FLOMAX* 0.4-mg once daily is recommended as the dose for the treatment of the signs and symptoms of BPH. It should be administered approximately one-half hour following the same meal each day.

For those patients who fall to respond to the 0.4-mg dose after two to four weeks of dosing, the dose of FLOMAX" can be increased to 0.8-mg once daily. If FLOMAX" administration is discontinued or interrupted for several days at either the 0.4-mg or 0.8-mg dose, therapy should be started again with the 0.4-mg once daily dose.

Caution: Federal (USA) law prohibits dispensing without a prescription FLOMAX' capsules should be stored at 20"-25" C (68" 77" F) Consult package insert before prescribing.

FL BS-MIT



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Yamanouchi

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