

# 'Green' Alternatives Posed for Preserving BMD

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GLASGOW, SCOTLAND — Soy products and dietary supplements containing a high level of flavonoids may be alternatives to chemoprevention of osteoporosis and prostate cancer, so long as consumption is moderated to limit the potential for side effects, investigators said at the 8th European Congress of Endocrinology.

Much of the evidence supporting the

benefits of dietary soy comes from epidemiologic studies and analyses of disease patterns in Asians who change their diets after migrating to the West, according to Eva Lydeking-Olsen, a nurse practitioner and nutritionist with the Institute for Optimum Nutrition in Copenhagen.

When it comes to bone protection, epidemiologic studies and double-blinded placebo-controlled trials of soy lasting at least 6 months have shown mixed results. Four of 12 such studies have shown no

benefits, as measured by dual-energy x-ray densitometry scans of bone mineral density (BMD), while eight have, said Ms. Lydeking-Olsen.

The eight showing a bone-protective effect focused on at-risk groups, so it was likely that continuing loss of bone mass in the control group affected the outcomes of the study, she said.

Consumption of 50-90 mg of isoflavones appears to have a beneficial effect, roughly the same as drinking two

glasses of soy milk per day, she said.

"In the case of soy foods it is advisable to ask the manufacturer about the amount of isoflavones in specific brands of soy milk and soy yogurt, and also use foods such as natural, roasted soy flakes—on muesli, mixed in hot cereal or sprinkled over the salad—or soy nuts as a snack, as very little [isoflavone is] lost in those natural products," she said in an interview.

Another expert, however, warned that there is evidence that behavior of isoflavones could potentially have the same negative effects as estrogen, such as stimulating growth of uterine and breast tissues, leading to tumors.

"There is good evidence that lifelong intake of these isoflavones can be beneficial," said Dr. Wolfgang Wuttke, professor of clinical and experimental endocrinology at the University of Göttingen. "But these are prepubertal effects.

"The evidence is so controversial that the [Food and Drug Administration] ... would never allow sale of these substances as a drug," said Dr. Wuttke "Why should I recommend substances which I am not sure are safe and might be useless?"

But when it comes to prostate cancer, Dr. Wuttke said that he believes there may be benefits for older men with increased isoflavone consumption.

Among the most studied of the isoflavones influencing prostate health is genistein, which may slow with the growth of prostate cells by influencing the hormone-metabolizing enzymes and reducing the sensitivity of the primary targets of androgen hormones such as the androgen receptor, said Dr. Helmut Klocker, a specialist in urology at Innsbruck (Austria) University Hospital.

Unlike with osteoporosis and soy, Dr. Klocker said there are no double-blinded placebo-controlled studies demonstrating the preventive effect of genistein.

"The problem with these [studies] is they would have to be performed over many years," he said in an interview. "To my knowledge, it is not clear if there is a beneficial effect at any [specific] time in life. There is also some evidence that exposure to genistein and related substances is most efficient during growing up and puberty, and even during embryogenesis. You can imagine that it is almost impossible to investigate this in controlled trials."

In a phase II trial sponsored by the National Cancer Institute, scientists are recruiting patients to test both the effectiveness and potential toxicity of genistein among men with stage I and stage II prostate cancer.

The trial plans to randomize 88 patients undergoing radical prostatectomy into two groups. One group will receive oral genistein once daily for 1-2 months, undergo the prostatectomy, and then continue the genistein regimen for 1-2 months afterward. The other group will undergo the prostatectomy first, and begin a 3-month genistein regimen 1 month after the surgery. The trial will test the reduction in prostate-specific antigen-positive cells in the operative field and quality of life at baseline and 1 and 3 months after surgery, Dr. Klocker said.

## BRIEF SUMMARY

The following is a brief summary. Before prescribing, please consult full prescribing information.

### WARNINGS

**Fatal Infusion Reactions:** Deaths within 24 hours of RITUXAN infusion have been reported. These fatal reactions followed an infusion reaction complex, which included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. (See WARNINGS and ADVERSE REACTIONS.)

Patients who develop severe infusion reactions should have RITUXAN infusion discontinued and receive medical treatment.

**Tumor Lysis Syndrome (TLS):** Acute renal failure requiring dialysis with instances of fatal outcome has been reported in the setting of TLS following treatment of non-Hodgkin's lymphoma (NHL) patients with RITUXAN. (See WARNINGS.)

**Severe Mucocutaneous Reactions:** Severe mucocutaneous reactions, some with fatal outcome, have been reported in association with RITUXAN treatment. (See WARNINGS and ADVERSE REACTIONS.)

### INDICATIONS

RITUXAN (rituximab) in combination with methotrexate is indicated to reduce signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

### CONTRAINDICATIONS

RITUXAN is contraindicated in patients with known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of this product. (See WARNINGS.)

### WARNINGS (See BOXED WARNINGS.)

**Severe Infusion Reactions (see BOXED WARNINGS, ADVERSE REACTIONS, and Hypersensitivity Reactions)**

RITUXAN has caused severe infusion reactions. In some cases, these reactions were fatal. These severe reactions typically occurred during the first infusion with time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion reactions may include urticaria, hypotension, angioedema, hypoxia, or bronchospasm, and may require interruption of RITUXAN administration. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and anaphylactic and anaphylactoid events. In the reported cases, the following factors were more frequently associated with fatal outcomes: female gender, pulmonary infiltrates, and chronic lymphocytic leukemia or mantle cell lymphoma.

**Management of severe infusion reactions:** The RITUXAN infusion should be interrupted for severe reactions. Medications and supportive care measures including, but not limited to, epinephrine, antihistamines, glucocorticoids, intravenous fluids, vasopressors, oxygen, bronchodilators, and acetaminophen, should be available and instituted as medically indicated for use in the event of a reaction during administration. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Patients requiring close monitoring during first and all subsequent infusions include those with pre-existing cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events and those with high numbers of circulating malignant cells ( $\geq 25,000/\text{mm}^3$ ) with or without evidence of high tumor burden. (See WARNINGS, Cardiovascular and ADVERSE REACTIONS.)

**Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections**

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with RITUXAN. The majority of patients received RITUXAN in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of RITUXAN and approximately one month after the last dose.

Persons at high risk of HBV infection should be screened before initiation of RITUXAN. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and for up to several months following RITUXAN therapy. In patients who develop viral hepatitis, RITUXAN and any concomitant chemotherapy should be discontinued and appropriate treatment including antiviral therapy initiated. There are insufficient data regarding the safety of resuming RITUXAN therapy in patients who develop hepatitis subsequent to HBV reactivation.

The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or postmarketing reports. The majority of patients received RITUXAN in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included JC virus [progressive multifocal leukoencephalopathy (PML)], cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of RITUXAN and have resulted in death.

### Hypersensitivity Reactions

RITUXAN has been associated with hypersensitivity reactions (non-IgE-mediated reactions), which may respond to adjustments in the infusion rate and in medical management. Hypotension, bronchospasm, and angioedema have occurred in association with RITUXAN infusion (see Severe Infusion Reactions). RITUXAN infusion should be interrupted for severe hypersensitivity reactions and can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Treatment of these symptoms with diphenhydramine and acetaminophen is recommended; additional treatment with bronchodilators or IV saline may be indicated. In most cases, patients who have experienced non-life-threatening hypersensitivity reactions have been able to complete the full course of therapy. (See DOSAGE and ADMINISTRATION.) Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines, and glucocorticoids, should be available for immediate use in the event of a reaction during administration. (See WARNINGS, Management of severe infusion reactions, and Cardiovascular, and ADVERSE REACTIONS.)

### Cardiovascular

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of RITUXAN. Patients with pre-existing cardiac conditions including arrhythmias and angina have had recurrences of these events during RITUXAN therapy and should be monitored throughout the infusion and immediate post-infusion period.

**Renal (See BOXED WARNINGS: Tumor Lysis Syndrome [TLS] and ADVERSE REACTIONS)**

RITUXAN administration has been associated with severe renal toxicity including acute renal failure requiring dialysis and in some cases, has led to a fatal outcome in hematologic malignancy patients. Renal toxicity has occurred in patients with high numbers of circulating malignant cells ( $>25,000/\text{mm}^3$ ) or high tumor burden who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and RITUXAN is not an approved treatment regimen. If this combination is used in clinical trials extreme caution should be exercised; patients should be monitored closely for signs of renal failure. Discontinuation of RITUXAN should be considered for those with rising serum creatinine or oliguria.

### Severe Mucocutaneous Reactions (See BOXED WARNINGS)

Mucocutaneous reactions, some with fatal outcome, have been reported in patients treated with RITUXAN. These reports include paraneoplastic pemphigus (an uncommon disorder which is a manifestation of the patient's underlying malignancy), Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of the reaction in the reported cases has varied from 1 to 13 weeks following RITUXAN exposure. Patients experiencing a severe mucocutaneous reaction should not receive any further infusions and seek prompt medical evaluation. Skin biopsy may help to distinguish among different mucocutaneous reactions and guide subsequent

treatment. The safety of readministration of RITUXAN to patients with any of these mucocutaneous reactions has not been determined.

**Concomitant use with biologic agents and DMARDs other than methotrexate in RA:** Limited data are available on the safety of the use of biologic agents or DMARDs other than methotrexate in patients exhibiting peripheral B cell depletion following treatment with rituximab. Patients should be closely observed for signs of infection if biologic agents and/or DMARDs are used concomitantly.

### PRECAUTIONS

#### Information for Patients

Patients should be provided the RITUXAN Patient Information leaflet and provided an opportunity to read it prior to each treatment session. Because caution should be exercised in administering RITUXAN to patients with active infections, it is important that the patient's overall health be assessed at each visit and any questions resulting from the patient's reading of the Patient Information be discussed.

#### Laboratory Monitoring

Because RITUXAN targets all CD20-positive B lymphocytes (malignant and nonmalignant), complete blood counts (CBC) and platelet counts should be obtained at regular intervals during RITUXAN therapy and more frequently in patients who develop cytopenias (see ADVERSE REACTIONS). The duration of cytopenias caused by RITUXAN can extend well beyond the treatment period.

#### Drug/Laboratory Interactions

There have been no formal drug interaction studies performed with RITUXAN. However, renal toxicity was seen with this drug in combination with cisplatin in clinical trials. (See WARNINGS, Renal.) In clinical trials of patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the pharmacokinetics of rituximab.

#### Immunization

The safety of immunization with live viral vaccines following RITUXAN therapy has not been studied and vaccination with live virus vaccines is not recommended. The ability to generate a primary or anamnestic humoral response to vaccination is currently being studied.

Physicians should review the vaccination status of patients with RA being considered for RITUXAN treatment and follow the Centers for Disease Control and Prevention (CDC) guidelines for adult vaccination with non-live vaccines intended to prevent infectious disease, prior to therapy. For patients with NHL, the benefits of primary and/or booster vaccinations should be weighed against the risks of delay in initiation of RITUXAN therapy.

**Use in patients with RA who had no prior inadequate response to TNF antagonists:** While efficacy of RITUXAN was supported in two well-controlled trials in patients with RA with prior inadequate responses to non-biologic DMARDs, a favorable risk/benefit relationship has not been established in this population. The use of RITUXAN in patients with RA who have no prior inadequate response to one or more TNF antagonists is not recommended. (See CLINICAL STUDIES, Rheumatoid Arthritis.)

**Retreatment in patients with RA:** Safety and efficacy of retreatment have not been established in controlled trials. A limited number of patients have received two to five courses (two infusions per course) of treatment in an uncontrolled setting. In clinical trials in patients with RA, most of the patients who received additional courses did so 24 weeks after the previous course and none were retreated sooner than 16 weeks.

#### Carcinogenesis, mutagenesis, impairment of fertility

No long-term animal studies have been performed to establish the carcinogenic potential of RITUXAN. Studies also have not been completed to assess mutagenic potential of RITUXAN, or to determine potential effects on fertility in males or females. Individuals of childbearing potential should use effective contraceptive methods during treatment and for up to 12 months following RITUXAN therapy.

#### Pregnancy Category C

An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Animals were administered rituximab via the intravenous route during early gestation (organogenesis period; post-coitum days 20 through 50). Rituximab was administered as loading doses on post-coitum days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on post-coitum days 29, 36, 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in exposures of 0.8-fold a human 2 g dose based on AUC. Although rituximab has been shown to cross the monkey placenta, there was no evidence of teratogenicity under the conditions of the experiment.

Nonteratogenic effects: Results from the embryo-fetal developmental toxicology study described above showed that rituximab treatment produced a decrease in lymphoid tissue B cells in the offspring of treated dams.

A subacute pre- and postnatal developmental toxicity study in cynomolgus monkeys was completed to assess developmental toxicity and the recovery of B-cells and immune function in infants exposed to rituximab in utero. Rituximab was administered from early gestation (post-coitum day 20) through lactation (post-partum day 28). Due to the possibility of anti-drug antibody development with such a long dosing period, the animals were divided into 3 sets of dosing periods: one set received rituximab (20 or 100 mg/kg weekly) from post-coitum day 20 through delivery and post-partum day 28 (~25 weeks); a second set received rituximab (20 or 100 mg/kg weekly) from post-coitum day 50 through post-coitum day 76 (8 weeks); a third set received rituximab (20 or 100 mg/kg weekly) from post-coitum day 76 through delivery and post-partum day 28 (~8 weeks). For each of these dosing periods, a loading dose was administered for the first 3 days of the period at doses of 15 or 75 mg/kg/day. The decreased B cells and immunosuppression noted in the offspring of pregnant animals treated with either 20 or 100 mg/kg/week rituximab showed a return to normal levels and function within 6 months post-birth. However, there are no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### Nursing Mothers

Rituximab was excreted in the milk of lactating cynomolgus monkeys. It is not known whether RITUXAN is excreted in human milk. Because human IgG is excreted in human milk and the potential for absorption and immunosuppression in the infant is unknown, women should be advised to discontinue nursing until circulating drug levels are no longer detectable. (See CLINICAL PHARMACOLOGY.)

#### Pediatric Use

The safety and effectiveness of RITUXAN in pediatric patients have not been established.

#### Geriatric Use

Among the 517 patients in the phase 3 RA study, 16% were 65 to 75 years old and 2% were 75 years old and older. The RITUXAN ACR 20 response rates in the older (age  $\geq 65$  years) vs. younger (age  $< 65$  years) patients were similar (53% vs. 51%, respectively). Adverse reactions, including incidence, severity, and type of adverse reaction were similar between older and younger patients.

#### ADVERSE REACTIONS

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 practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The following serious adverse reactions, some with fatal outcomes, have been reported in patients treated with RITUXAN (see BOXED WARNINGS and WARNINGS): severe or fatal infusion reactions, tumor lysis syndrome, severe mucocutaneous reactions, hepatitis B reactivation with fulminant hepatitis, other viral infections, hypersensitivity reactions, cardiac arrhythmias, renal toxicity, bowel obstruction and perforation.

#### Post-Marketing Reports

The following adverse reactions have been identified during post-approval use of RITUXAN. 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. Decisions to identify these

reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to RITUXAN.

**Hematologic:** prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia, hyperviscosity syndrome in Waldenström's macroglobulinemia.

**Cardiac:** fatal cardiac failure.

**Immune/Autoimmune Events:** uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis and vasculitis with rash.

**Infection:** increased in fatal infections in HIV-associated lymphoma.

**Skin:** severe mucocutaneous reactions.

**Gastrointestinal:** bowel obstruction and perforation.

#### Adverse Reactions in Patients with Rheumatoid Arthritis

In general, the adverse events observed in patients with RA were similar in type to those seen in patients with non-Hodgkin's lymphoma (see WARNINGS, PRECAUTIONS and other sections under ADVERSE REACTIONS). Specific safety considerations in this indication are discussed below.

Where specific percentages are noted, these data are based on 938 patients treated in Phase 2 and 3 studies of RITUXAN (2 × 1000 mg) or placebo administered in combination with methotrexate.

**Table 1**  
Incidence of All Adverse Events\* Occurring in  $\geq 2\%$  and at Least 1% Greater Than Placebo Among Rheumatoid Arthritis Patients in Clinical Studies Up to Week 24 (Pooled)

Preferred Term	Placebo + MTX N=398 n (%)	RITUXAN + MTX N=540 n (%)
Abdominal Pain Upper	4 (1)	11 (2)
Anxiety	5 (1)	9 (2)
Arthralgia	14 (4)	31 (6)
Asthenia	1 (<1)	9 (2)
Chills	9 (2)	16 (3)
Dyspepsia	3 (<1)	16 (3)
Hypercholesterolemia	1 (<1)	9 (2)
Hypertension	21 (5)	43 (8)
Migraine	2 (<1)	9 (2)
Nausea	19 (5)	41 (8)
Parosmia	3 (<1)	12 (2)
Pruritus	5 (1)	26 (5)
Pyrexia	8 (2)	24 (5)
Rhinitis	6 (2)	14 (3)
Throat Irritation	0 (0)	11 (2)
Upper Respiratory Tract Infection	23 (6)	37 (7)
Urticaria	3 (<1)	12 (2)

\*Coded using MedDRA.

#### Infusion Reactions

In RITUXAN RA placebo-controlled studies, 32% of RITUXAN-treated patients experienced an adverse event during or within 24 hours following their first infusion, compared to 23% of placebo-treated patients receiving their first infusion. The incidence of adverse events during the 24-hour period following the second infusion, RITUXAN or placebo, decreased to 11% and 13%, respectively. Acute infusion reactions (manifested by fever, chills, rigors, pruritus, urticaria/rash, angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated hypotension or hypertension) were experienced by 27% of RITUXAN-treated patients following their first infusion, compared to 19% of placebo-treated patients receiving their first placebo infusion. The incidence of these acute infusion reactions following the second infusion of RITUXAN or placebo decreased to 9% and 11%, respectively. Serious acute infusion reactions were experienced by <1% of patients in either treatment group. Acute infusion reactions required dose modification (stopping, slowing or interruption of the infusion) in 10% and 2% of patients receiving rituximab or placebo, respectively, after the first course. The proportion of patients experiencing acute infusion reactions decreased with subsequent courses of RITUXAN. The administration of IV glucocorticoids prior to RITUXAN infusions reduced the incidence and severity of such reactions, however, there was no clear benefit from the administration of oral glucocorticoids for the prevention of acute infusion reactions. Patients in clinical studies also received antihistamines and acetaminophen prior to RITUXAN infusions.

#### Infections

In RA clinical studies, 39% of patients in the RITUXAN group experienced an infection of any type compared to 34% of patients in the placebo group. The most common infections were nasopharyngitis, upper respiratory tract infections, urinary tract infections, bronchitis, and sinusitis. The only infections to show an absolute increase over placebo of at least 1% were upper respiratory tract infections, which affected 7% of RITUXAN-treated patients and 6% of placebo-treated patients and rhinitis, which affected 3% of RITUXAN-treated patients and 2% of placebo-treated patients.

The incidence of serious infections was 2% in the RITUXAN-treated patients and 1% in the placebo group. One fatal infection (bronchopneumonia) occurred with rituximab monotherapy during the 24-weeks placebo-controlled period in one of the Phase 2 RA studies.

#### Cardiac Events

The incidence of serious cardiovascular events in the double-blind part of the clinical trials was 1.7% and 1.3% in RITUXAN and placebo treatment groups, respectively. Three cardiovascular deaths occurred during the double-blind period of the RA studies including all rituximab regimens (3/769=0.4%) as compared to none in the placebo treatment group (0/389).

Since patients with RA are at increased risk for cardiovascular events compared with the general population, patients with RA should be monitored throughout the infusion and RITUXAN should be discontinued in the event of a serious or life-threatening cardiac event.

#### Immunogenicity

A total of 54/990 patients (5%) with RA tested positive for HACA. Of these, most became positive by week 24. Following the first course, however, some became positive at week 16 or after 24 weeks. Some patients tested positive after the second course of treatment. Limited data are available on the safety or efficacy of RITUXAN retreatment in patients who develop HACA. One of 10 HACA-positive patients who received retreatment with RITUXAN experienced a serious acute infusion reaction (bronchospasm). The clinical relevance of HACA formation in rituximab-treated patients is unclear.

#### OVERDOSAGE

There has been no experience with overdosage in human clinical trials. Single doses of up to 500 mg/m<sup>2</sup> have been given in dose-escalation clinical trials.

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