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Clinical Oncology
A monthly update of developments in cancer treatment and research [ALERT]

ILLUSTRATIVE CASE SERIES

Current Approaches for Treating Patients with Fludarabine-resistant CLL

By Jerome Yates, MD
Hematology/Immunology Unit, National Institute on Aging, NIH
Dr. Yates reports no financial relationships relevant to this field of study.

A 58-YEAR-OLD RETIRED SCHOOL PRINCIPAL WAS SEEN IN the office because of malaise and weight loss. He had been well until 4 years ago when he was discovered, at a routine annual exam, to have lymphocytosis. At that time, he was asymptomatic and was without lymphadenopathy, splenomegaly, anemia, or thrombocytopenia. His white blood count was 17,000/cu mm, with 90% small lymphocytes. It was elected to observe initially, and he was followed at regular intervals. His white count, initially stable, rose gradually during the second year after diagnosis, and although his hemoglobin and platelet counts remained normal, he began to experience constitutional symptoms, including fatigue and night sweats. Approximately 24 months after diagnosis, he was started on chemotherapy with fludarabine, cytoxan, and rituximab (FCR). At that time, his lymphocyte count was approximately 60,000/cu mm and a CT scan revealed axillary and retroperitoneal nodes, but not bulky. The spleen was not enlarged. Peripheral blood and bone marrow were examined for prognostic markers, and his CLL cells were found to have unmutated IVGH, and approximately 40% expressed CD38. Furthermore, cytogenetic studies revealed a 17p deletion.

Chemotherapy consisted of rituximab 375 mg/m^2 on day 1, fludarabine 30 mg/m^2 days 1-3, and cytoxan 250 mg/m^2 on days 1-3. Treatment was continued for a total of six monthly cycles; it was tolerated without delays or dose reductions. His lymphocyte count dropped to 4,000/cu mm, and there was complete resolution of lymphadenopathy (by CT). Upon completion of therapy, the patient felt well,

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but blood counts continued to rise, and by 3 months after chemotherapy, his lymphocyte count was 30,000 and constitutional symptoms returned. It was decided to give two additional cycles of FCR. Once again, he experienced a reduction in lymphocyte number, but the response was transient. He was seen on this occasion for consideration of second-line CLL therapy.

CASE DISCUSSION

Treatment with purine analogues, such as fludarabine, either alone or in combination, is usually highly effective in the management of chronic lymphocytic leukemia. Although in retrospect one might question the delay in starting therapy in this case, treatment delay in asymptomatic stage 0 CLL remains the standard approach.[1] Choosing the FCR regimen also was most appropriate, as such treatment has been associated with overall response rates in excess of 90% and 5-year disease-free survival of approximately 70%.[2,3] However, there remains much consternation on what to do when responses to FCR are sub-optimal. Responses may be achieved with other combinations, particularly with the addition of an anthracycline but, in general, the likelihood of durable remission is low with such an approach. In a patient such as the one presented, alternative approaches should be considered. Those that are currently available and that would be on my list include the following:

Alemtuzumab (Campath®) is a humanized monoclonal antibody directed at the CD52 molecule that has demonstrated activity in fludarabine-resistant CLL and is FDA approved for patients who have previously been treated with alkylating agents and for whom fludarabine has failed. In a multicenter clinical trial of such patients (n = 93), the overall response rate was 33% (2% CR, 31% PR).[4] Alemtuzumab was administered on a dose-escalation schedule toward a target dose of 30 mg three times weekly, for a maximum of 12 weeks. It took, on average, 1.5 months to observe response, and the median time to disease progression, including all patients, was 4.7 months. For responders, the median time to progression was 9.5 months. A number of other trials have reported similar findings or even slightly better responses.[5-7] For a review of Alemtuzumab and its use in refractory CLL, see reference 8. Notably, treatment is associated with T-cell immune deficiency, and antiviral/anti-pneumocystis prophylaxis is essential to achieve optimal results.

Lenolidomide (Revlimid®) is an immunomodulating drug with demonstrated activity for patients with multiple myeloma and myelodysplastic syndrome. Treatment with lenalidomide at 25 mg orally on days 1 through 21 of 28-day cycles produced one CR and six PRs among 23 fludarabine-resistant CLL patients,[9] and similar results have been observed elsewhere.[10] In general, adverse events associated with lenalidomide treatment at this dose include fatigue, thrombocytopenia, neutropenia, and gastrointestinal symptoms.

Allogeneic Stem Cell Transplant is another alternative for patients who have an appropriate matched donor and are sufficiently fit to withstand the procedure. There have been several published reports, including those using reduced-intensity conditioning regimens that have reported recurrence rates ranging from 5% to 28% at 2 years.[11-13]

An approach that I might take for this 58-year-old patient with fludarabine-resistant CLL would be to initiate second-line treatment with lenalidomide while performing the necessary studies to refer to a transplant center for consideration of allogeneic transplant. In my opinion, this would provide the greatest chance for achieving a durable remission. ■

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RAPID REVIEW

Hypereosinophilia: Current Classification and Treatment Approaches

By William B. Ershler, MD

With the development of an increased understanding of cellular biology, in general, and the regulation of eosinophils, in particular, the heterogeneous diagnosis of hypereosinophilic Syndrome (HES) has now been better defined and a classification system has been developed with clear clinical implications.[1] Most commonly, eosinophilia is secondary and the result of parasitic infections, vasculitis, allergy, or drugs. Accordingly, the diagnosis and management are often undertaken by infectious-disease specialists or allergists. However, when a cause for secondary eosinophilia is not readily apparent, it is reasonable to undertake a focused diagnostic approach to classify the condition and provide appropriate management. By definition, patients with hypereosinophilia have eosinophil counts > 1,500/uL persisting for at least six consecutive months, and are considered to have HES if there is end organ impairment or dysfunction related to the hypereosinophilia.[2]

HYPEREOSINOPHILIA

Our understanding of the pathogenesis of primary eosiniophilic disorders has evolved dramatically over the past decade, and there are currently three major subsets considered, two of which are demonstrably clonal. These three categories are: 1) patients with chronic eosinophilic leukemia; 2) patients with IL-5/Th2 lymphocyte-mediated clonal hypereosinophilia (sometimes referred to as "lymphoproliferative" HES); and, idiopathic eosinophilia without evidence for clonal proliferation.[1,3] Thus, patients with "idiopathic" hypereosinophilia include both those who have associated organ impairment (HES) and those for whom the finding is not associated with organ involvement. However, excluded from the "idiopathic" category are those with either secondary eosinophilia or those with clonal eosinophilia.

There are now well-described specific mutations associated with each of the two clonal hypereosinophil-

Table 1: Approach to Eosinophilia

History	Travel, infections, allergies, other medical conditions, drugs	Rule out secondary eosinophilia	Treat the primary cause
Physical examination	Signs of infection, hepatosplenomegaly, lymphadenopathy, cardiac murmur		
Routine Laboratories/ Imaging studies	Routine chemistries, stool for ova/parasites, serological tests for suspected pathogens, troponin, chest X-ray, CT scan		
Peripheral blood	Screen for FIP1L1-PDGFRA using FISH or RT-PCR	Mutation present, diagnosis of FIP1L1-PDGFRA clonal eosinophilia established, proceed to treatment	Imatinib
	Flow cytometry for lymphocyte phenotype	If abnormal or clonal lymphocytes present, 'lymphocytic' variant eosinophilia	Chemotherapy, MAb (anti-IL5, anti CD52)
	T cell Receptor gene re-arrangement studies		
Bone marrow	Histopathology	Dysplastic features, increased blasts (chronic eosinophilic leukemia-NOS, or other myeloid neoplasm)	Treat underlying myeloid malignancy
	Cytogenetics	5q33 translocation (PDGFRB rearranged clonal eosinophilia)	Imatinib
		8p11 translocation (FGR1-rearranged clonal eosinophilia)	Aggressive lymphoma management
All of the above negative		Idiopathic eosinophilia (including HES)	Treatment aimed at avoiding organ damage (Steroids, Interferon, cytotoxic drugs, others)

For a more comprehensive discussion of treatment options, see references 1 and 10.

Source: Adapted from Teferri, et al.[1]

ias, and these include mutations and rearrangements of *PDGFRA*, *PDGFRB*, and *FGFR1* genes. Efforts at correct classification are warranted, as there is now sufficient information that such will help guide appropriate treatment choices (*Table 1*).

Thus, HES was once used to describe primary eosinophilia, but currently the term HES is now reserved for those with idiopathic eosinophilia and end organ damage resulting from the high eosinophil number.

MANAGEMENT

Once secondary eosinophilia is ruled out, as best possible, treatment considerations are directed by category. For patients in whom clonal eosinophilia is associated with the fusion gene *FIP1L1-PDGFRA*, treatment should be initiated with the tyrosine-kinase inhibitor imatinib mesylate, as this has proven highly effective, even at very low doses (e.g., 100 mg/day, or even less).[4-6] Imatinib therapy also is effective for clonal eosinophilia associated with *PDGFRB* mutations, although higher doses might be required.[7] In contrast, *FGFR1*-rearranged clonal eosinophilia presents as an aggressive myeloproliferative disease and is associated with T-cell lymphoblastic lymphoma and/or progression to AML. Patients with this disorder need to be treated aggressively, but even so, durable responses are uncommon.

Novel therapies have been studied for patients with each type of eosinophilia, and these include alternative kinase inhibitors (e.g., nilotinb, surafenib), and

monoclonal antibodies to IL-5 (mepolizumab) and CD52 (alemtuzumab). For patients refractory to these approaches, they have been treated with some success with chemotherapy. For patients with idiopathic eosinophilia and tissue injury mediated by eosinophils (i.e., HES), the goal of therapy is to reduce eosinophil number, and corticosteroid therapy has been most commonly employed. Chemotherapy, such as with cladarabine, has been of some benefit, as has treatment with mepolizumab or alemtuzumab. Imatinib, unfortunately, has little role in this setting,[8] although occasional reports have been positive.[9]

SUMMARY

As the molecular pathogenesis of eosinophilia is increasingly understood, it is apparent that accurate diagnosis is of critical importance for optimal management. Specifically, the discovery of FIP1L1-PDGFRA has transformed both the understanding and management of at least one form of eosinophilia previously considered HES, and has led to a much greater understanding of the management of other forms. ■

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ABSTRACT & COMMENTARY

Study Evaluates Autologous Transplant for Rare Myelomas

By Andrew S. Artz, MD

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Dr. Artz reports no relationships relevant to this field of study.

Synopsis: *Very limited data are available on autologous transplant outcomes for uncommon or rare multiple myeloma (MM) subtypes. The authors evaluated the European Group for Blood and Marrow Transplantation Myeloma Database comprising outcomes for the following subtypes: 379 IgD, 13 IgE, 72 IgM, and 976 non-secretory. Compared to more than 20,000 common myelomas, such as IgG, IgA, or Bence Jones Protein MM, IgD manifested inferior overall survival. IgE and IgM also fared poorly, but small numbers limited statistical comparisons. Non-secretory MM demonstrated similar OS to typical MM. Although survival of IgD, IgE, and IgM MM is worse after autologous transplant than typical MM, survival is reasonable compared to the poor outcomes previously reported. Novel approaches with maintenance are of particular interest for rare myelomas to improve outcomes.*

Source: Morris C, et al. Efficacy and outcome of autologous transplant for rare myelomas. *Haematologica*. 2010; 95:2126-2133.

Over 90% of multiple myeloma (MM) patients will have either an IgG, IgA, or Bence-Jones Protein only. IgD and non-secretory MM are less common, whereas IgM and IgE are rare. Overall survival for non-secretory MM is thought to be similar to typical MM, whereas outcomes for IgD MM are poor.[1,2] IgE and IgM are thought to fare poorly, although cases are rare. Autologous stem-cell rescue after high-dose chemotherapy remains an important tool in the treatment of MM.[3] Limited data are available addressing outcomes after high-dose therapy and autologous transplantation for less common, or rare, MM subtypes.

The authors reviewed autologous transplant from the European Group for Blood and Marrow Transplantation, the primary transplant registry for Europe. Among the 22,244 transplants between 1986 and 2007, there were 976 non-secretory (4.4%), 379 IgD (1.7%), 72 IgM (0.3%), and 13 IgE (0.1%). The vast majority of transplants for MM were for IgG, IgA, and Bence-Jones Protein, for whom the median survival was 62.3 months. In comparison, IgD MM survival was shorter at 43.5 months ($p = 0.0001$), despite having high complete remissions, implying a higher relapse rate. Transplant-related mortality also was increased. Overall survival for IgM at 44.7 months mirrored outcomes for IgD MM. IgE showed the lowest median survival at 34 months, although the small size of both IgM and IgE limited statistical conclusions. Non-secretory MM showed significantly improved progression-free survival, but the median overall survival of 64.6 months did not differ from the 62.3 months for common myelomas.

■ COMMENTARY

Autologous transplantation remains a mainstay for adequately fit MM patients based on randomized trials demonstrating improved survival. As expected, data are primarily derived from common ideotypes of MM: IgG, IgA, and those with Bence-Jones Proteins. To assess outcomes after autologous transplant for less-common myelomas, the authors evaluated the European transplant registry, contrasting infrequent myelomas of non-secretory, IgD, IgE, and IgM to the more common variants. Non-secretory myelomas showed better progression-free survival and similar overall survival to typical MM. However, the authors accurately point out the lack of sensitive paraprotein measures in non-secretory cases (the cohort was primarily before light chain assays) to assess response delays, formally declaring progressive disease and may exclude such patients from clinical trials. We can now more confidently counsel patients with non-secretory MM applying the reported clinical trial data for MM.

The worse survival for IgD, IgE, and IgM MM compared to typical MM is the most novel finding. The small numbers for IgM and particularly IgE limit reliable statistical comparisons, whereas the reduction in survival by approximately 19 months for IgD was clinically and statistically significant. The more germane question of whether autologous transplant is beneficial vs. conventional treatment cannot be answered in this study. As an observational study, the data clearly have limitations related to selection bias as those undergoing transplant are typically younger and/or healthier.

However, as these rare myelomas generally exhibit poorer overall survival than observed in this study and transplant benefits more common myeloma subtypes, it is reasonable to maintain transplant in the overall therapeutic strategy. Clearly, the introduction of novel agents such as bortezomib and thalidomide has remarkably altered the therapeutic landscape. Rather than excluding the need for transplant, the addition of novel agents for maintenance therapy after transplant has provided preliminary but highly promising results. The poor outcomes for rare myelomas emphasize the need in future studies to determine if reduced progression from maintenance therapy will extend to non-secretory and rare myelomas.

In conclusion, high-dose therapy followed by autologous transplant results in similar survival for non-secretory MM compared to the common ideotypes of IgG, IgA, and Bence-Jones Protein. The rare IgG, IgE, and IgM myelomas fare worse relative to common myeloma but best historical non-transplant outcomes. Thus, autologous transplant should still be entertained for less common myelomas, just as in the more common forms. ■

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ABSTRACT & COMMENTARY

Cetuximab and First-cycle Rash: Correlation with NSCLC Outcomes

By William B. Ershler, MD

Synopsis: *The occurrence of skin rash in patients receiving cetuximab is common, and for patients with colon cancer, this has been associated with better clinical outcomes. In a multicenter, phase III trial (FLEX), cetuximab combined with chemotherapy, compared with chemotherapy alone was associated with better overall survival for patients with EGFR+ NSCLC, although the improvement was small. In the current report, a post-hoc analysis was undertaken to determine if the occurrence of rash conferred similar favorable prognostic information for patients with lung cancer. For those who developed rash during the first cycle, overall and progression-free survival was greater than for those receiving cetuximab / chemotherapy but who did not develop rash, or for those who received chemotherapy without cetuximab. Thus, as for cetuximab treatment for colon cancer, the appearance of rash may confer favorable prognosis for treated patients with lung cancer.*

Source: Gatzemeier U, et al. First-cycle rash and survival in patients with advanced non-small-cell lung cancer receiving cetuximab in combination with first-line chemotherapy: A subgroup analysis of data from the FLEX phase 3 study. *Lancet Oncology.* 2011;12:30-37.

Cetuximab, a monoclonal antibody directed at epidermal growth factor receptor (EGFR) has been approved for treatment of colorectal cancer and, more recently, head and neck cancer. The clinical experience in those settings has suggested that patients who develop skin rash seem to have a greater chance of experiencing favorable outcomes.[1,2] A randomized, phase III trial was undertaken to establish whether cetuximab (Erbitux®) would be effective as an adjunct to cisplatin/vinorelbine for patients with advanced non-small cell lung cancer whose tumors expressed EGFR. This multicenter trial (First-Line Erbitux in Lung Cancer [FLEX]) enrolled 1,125 patients and demonstrated a modest improvement in overall survival for the group receiving cetuximab with the two chemotherapy agents compared to the group receiving chemotherapy alone.[3] Consistent with the clinical experience of drugs in this class administered for other conditions, the main cetuximab-related side effect was an acne-like rash. The current research was undertaken to determine whether those who developed the typical acne-like rash during the first cycle were more likely to benefit from treatment. For this, a post-hoc analysis was performed on the data from the FLEX study.

For this, the investigators assessed if the development of acne-like rash in the first 21 days of treatment (first-cycle rash) was associated with improved clinical outcome, on the basis of patients in the intention-to-treat population alive on day 21. At that point (day 21), there were 518 patients in the chemotherapy plus cetuximab group — 290 of whom had first-cycle rash — and 540 patients in the chemotherapy alone group. Patients in the chemotherapy plus cetuximab group with first-cycle rash had significantly prolonged overall survival compared with patients in the same treatment group without first-cycle rash (median 15.0 months [95% CI 12.8–16.4] vs. 8.8 months [7.6–11.1]; hazard ratio [HR] 0.631 [0.515–0.774]; $p < 0.0001$). Corresponding significant associations also were noted for progression-free survival (median 5.4 months [5.2–5.7] vs. 4.3 months [4.1–5.3]; HR 0.741 [0.607–0.905]; $p = 0.0031$) and response rate (44.8% [39.0–50.8] vs. 32.0% [26.0–38.5]; odds ratio 1.703 [1.186–2.448]; $p = 0.0039$). Overall survival for patients without first-cycle rash was similar to that of patients who received chemotherapy alone (median 8.8 months [7.6–11.1] vs. 10.3 months [9.6–11.3]; HR 1.085 [0.910–1.293]; $p = 0.36$). The significant overall-survival benefit for patients with first-cycle rash vs. without was seen in all histology subgroups.

The findings from the FLEX trial indicated improved survival for patients with NSCLC who received cetuximab in combination with a standard chemotherapy regimen, but improvement was modest and the treatment very expensive, leading at least some to wonder whether this drug will have a role in the standard approach to this disease.[4] A disappointing feature of the FLEX study was the inability to predict from genetic or molecular mark-

ers which EGFR+ lung-cancer patients would benefit. Nonetheless, the appearance of rash during the first cycle, as detailed in this report, may be a significant lead in that direction, as first-cycle rash might be a surrogate clinical marker that could be used to tailor cetuximab treatment for advanced NSCLC to those patients who would be most likely to derive a significant benefit.

■ COMMENTARY

Yet, as pointed out in the accompanying editorial by Francesco Perrone, there remain some fundamental questions.[5] He points out that although it would be nice to conclude that patients who develop rash in response to cetuximab treatment are those who are likely to benefit, the data are insufficient to support that conclusion. In the FLEX study, cetuximab treatment with chemotherapy was only slightly better than chemotherapy alone, but the difference was quite dramatic for the subset that developed rash and, correspondingly, those who did not develop rash fared worse. Thus, it could be that the development of rash in response to cetuximab identifies those with more favorable prognosis, and that the drug has little or no effect on the tumor, per se. It will take a well-designed clinical trial to sort this out; in the meantime, the use of cetuximab for patients with NSCLC must be considered investigational. ■

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CME Questions

4. For patients with fludarabin-resistant CLL, which treatment option is associated with the greatest risk for infection?

a. Lenalidomide 25 mg, orally for 21 days each month.
b. Cyclophosphamide 500 mg/m^2 IV every 21 days.
c. Alemtuzumab 30 mg IV 3 times weekly for 12 weeks.
d. Rituximab 375 mg/m^2 IV weekly for 4 weeks.

5. Imatinib mesylate has proven effective in the treatment of which of the following disorders?

a. Idiopathic eosinophilia associated with tissue injury (HES).
b. Clonal eosinophilia-associated with FIP1L1-PDGRA.
c. Clonal eosinophilia associated with 8p11 translocation (FGFR1 rearrangement)
d. 'Lymphocytic' variant hypereosinophilia
e. All of the above

6. What are the outcomes after autologous transplant for less common myelomas compared to the common IgG, IgA, and Bence-Jones Protein ideotypes?

a. Non-secretory MM has inferior response rates.
b. Non-secretory MM has similar survival.
c. Survival for IgD is worse.
d. Very few IgE patients were transplanted, limited inferences.
e. B, C, and D

Answers: 4. (c); 5. (b); 6. (e)

CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss the most recent information regarding diagnosis and treatment of various types of cancer;
- describe current prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- describe new advances in the field of oncology.

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Immunochemical FOBT and low-dose aspirin

Source: Brenner H, et al. Low-dose aspirin use and performance of immunochemical fecal occult blood tests. *JAMA* 2010;304:2513-2520.

IMMUNOCHEMICAL FECAL OCCULT BLOOD testing (i-FOBT) is becoming increasingly popular as a screening tool for colorectal cancer (CRC). At the same time, the number of persons taking long-term low-dose aspirin (ASA) for CV disease risk reduction is also increasing. Concern has been expressed that the predictable increase in GI bleeding associated with ASA would decrease the specificity of i-FOBT by increasing false positives. At the same time, it has been suggested that consequences of i-FOBT to detect upper GI bleeding may have been overestimated, since the globin chains detected by i-FOBT typically are degraded progressively during passage through the GI tract, and are hence less available for i-FOBT identification than bleeding more distal in the GI tract. Finally, utilization of ASA might also increase the risk of bleeding of CRC, thus enhancing likelihood of detection.

To assess the relationship between ASA, i-FOBT, and results of CRC screening, Brenner et al reported on almost 2000 adults who underwent CRC screening, 12% of whom were regular ASA users.

Sensitivity (the number of positive tests in persons confirmed to have advanced GI neoplasms) of i-FOBT was greater in ASA users than non-users. i-FOBT specificity (the number of negative tests in persons without advanced GI neoplasms) was minimally reduced.

Chronic low-dose ASA does not appear to compromise the ability of i-FOBT to detect advanced GI neoplasia, with a modest decrease in specificity. ■

Aerobic vs resistance exercise for type 2 diabetes

Source: Church T, et al. Effects of aerobic and resistance training on hemoglobin A1c in patients with type 2 diabetes. *JAMA* 2010;304:2253-2262.

MOST PERSONS WITH TYPE 2 DIABETES (DM2) are overweight or obese. Exercise is routinely advised for DM2, although whether a particular method of exercise has an advantage for optimization of glycemic control is not well defined.

Church et al compared the effects of aerobic exercise (AER), resistance training (RES), or the combination (AER + RES) vs placebo in previously sedentary mid-life DM2 adults (mean age = 56 years). Participants engaged in the prescribed activities for 9 months. The primary outcome was change in A1c from baseline.

At the conclusion of the trial, only the AER + RES provided statistically significant reduction in A1c compared to placebo; AER alone or RES alone did not.

It would be unfortunate if clinicians were to interpret this trial as indicating a lack of value of either AER or RES alone. All exercise groups had favorable changes in anthropomorphic metrics, and exercise has been shown to be associated with a favorable impact upon cardiovascular risk in large population studies, an effect that may be independent of glycemic effects. ■

Atrial fibrillation risk: Choose your parents wisely

Source: Lubitz SA, et al. Association between familial atrial fibrillation and risk of new-onset atrial fibrillation. *JAMA* 2010;304:2263-2269.

A FAMILIAL COMPONENT CONTRIBUTES to atrial fibrillation (a-FIB) risk, such that independent of other risk factors (e.g., hypertension), having a first-degree relative with a-FIB increases risk.

Using data from participants (n = 11,971) in the Framingham Heart Study, Lubitz et al examined the relationship between having a first-degree relative (sibling or parent) with a-FIB and subsequent development of a-FIB during an 8-year window of observation.

Subjects with a positive family history had an increased risk of a-FIB compared to those without a family history (5.8% vs 3.1% over 8 years). Risk increased further with the number of family members affected by a-FIB. The younger the age of a-FIB onset in a family member, the greater the increase in a-FIB risk.

Overall, having a positive family history for a-FIB increased risk of new-onset a-FIB by 40%. Of all risk factors for a-FIB, hypertension is responsible for the largest population-attributable risk; whether treatment of hypertension in persons with demonstrated increased

risk for a-FIB because of family history might provide reduction in a-FIB risk remains to be determined. ■

The effects of obesity upon activity of short-acting insulin analogs

Source: Gagnon-Auger M, et al. Dose-dependent delay of the hypoglycemic effect of short-acting insulin analogs in obese subjects with type 2 diabetes: A pharmacokinetic and pharmacodynamic study. *Diabetes Care* 2010;33:2502-2507.

The most recent ADA/EASD algorithm for management of type 2 diabetes (DM2) indicates basal insulin as an appropriate next step if glycemic goals are not attained with metformin and lifestyle interventions. After fasting glucose levels are controlled on basal insulin regimens, it is common to use prandial bolus insulin (especially short-acting insulin analogs) if A1c goals have not been reached. The activity profile of short-acting insulin analogs has been established by trials in either lean healthy subjects or type 1 diabetics; neither population may be pharmacokinetically or pharmacodynamically concordant with DM2, and most are overweight or obese. To examine these issues, obese DM2 subjects (n = 7) received lispro insulin and were monitored for time to peak insulin concentration, maximal attained insulin concentration, and efficacy for reducing glucose.

Absorption of low-dose lispro (10 units) was similar in DM2 and controls, but its hypoglycemic effect was less in obese persons. At higher doses (30 units and 50 units), however, both absorption and efficacy were diminished in obese DM2 subjects. The authors challenge the current perceptions of the utility of short-acting insulin analogs in DM2, reminding us that the purpose of prandial insulin is to provide rapid rise and rapid glucose-lowering effects, both of which appear to be diminished in obese individuals. In any case, these data confirm that clinicians might anticipate proportionately less "bang-for-the-buck" as they up-titrate short-acting insulin analog doses in obese DM2. ■

Capitalizing on the second-meal effect in type 2 diabetes

Source: Chen JM, et al. Utilizing the second-meal effect in type 2 diabetes: Practical use of a soya-yogurt snack. *Diabetes Care* 2010;33:2552-2554.

It is probably not widely known that Mom was right — at least as it pertains to diabetes — that you should NOT skip breakfast. Why? Because of the "second-meal effect," a little-recognized physiologic response that can have a potentially favorable effect on glucose.

The way the "second-meal effect" works is like this: When breakfast is eaten, the degree of hyperglycemia seen after lunch is less than if the same amount of calories are given without having eaten breakfast. It has been suggested that the improved glucose level is related to a reduction in preprandial free fatty acids, which allows for greater storage of muscle glycogen during a second meal (and hence a greater disappearance of glucose from the plasma). This phenomenon occurs in both diabetic and non-diabetic individuals. Based upon this observation, Chen at al hypothesized that perhaps providing a pre-breakfast snack would reduce post-breakfast hyperglycemia.

Diabetic subjects (n = 10) were administered a snack of soya beans and yogurt 2 hours before breakfast. For scheduling convenience, the snack was administered at 8 am, and breakfast at 10 am.

Plasma glucose 2 hours after breakfast was significantly lower in the group who received the snack. Since postprandial glucose levels have been associated with adverse cardiovascular outcomes in diabetics, it might be both desirable and possible to manipulate post-meal hyperglycemia without using medications. ■

Seeking the best diet for weight-loss maintenance

Source: Larsen TM, et al. Diets with high or low protein content and glycemic index for weight loss maintenance. *N Engl J Med* 2010;363:2102-2013.

Identifying the "best" diet to achieve and maintain weight loss in overweight persons has been an elusive task. Even if a person is successful at reducing weight using a highly calorie-restricted diet over the short term, the choice of a preferred maintenance diet over the long term is ill-defined.

Larsen et al enrolled overweight adults who had successfully lost at least 8% of their initial body weight, and randomized them into diets based upon protein content and glycemic index. Five subgroups were thus defined based upon high or low protein (PRO) and glycemic index (GIN): high GIN + high PRO, high GIN + low PRO, low GIN + high PRO, low GIN + low PRO, and control). All subjects followed their respective diets for 26 weeks.

Both high PRO and low GIN were independently associated with lesser weight regain. Overall, adherence to diet and maintenance of weight loss was best with the high PRO + low GIN diet. It is possible that even greater benefit could have been achieved in relation to protein, because the actual separation of protein content between high PRO and low PRO of 5.4% was substantially less than the intended 12%. ■

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Statin Use in Patients with Abnormal Liver Function

In this issue: Statins and liver function; dosing timing for thyroxine; rivaroxaban for VTE, DVT, and stroke; echinacea and the common cold; and FDA actions.

Statins and liver function

Most physicians are hesitant to use statins in patients with abnormal liver function tests (ALT or AST less than three times the upper limit of normal). A new study suggests that not only are statins safe and effective, they may improve liver abnormalities in patients with fatty liver. In a study recently published in the *Lancet*, 437 patients enrolled in the Greek Atorvastatin and Coronary Heart Disease Evaluation study population were noted to have moderately abnormal liver tests at baseline, which were possibly associated with non-alcoholic fatty liver disease. Of that group, 227 were treated with a statin (atorvastatin) and 210 were not. Patients treated with a statin had substantial improvement in liver tests ($P < 0.0001$), whereas the group not treated with a statin had further increases in liver enzyme concentrations. Cardiovascular events occurred in 10% of atorvastatin-treated patients vs 30% of the non-statin group (60% relative risk reduction; $P > 0.0001$). This was a greater improvement in benefit than seen in patients with normal liver function tests. Fewer than 1% of the participants who received a statin had to discontinue statin treatment because of transaminase concentrations more than three times the upper limit of normal. The authors concluded that "statin treatment is safe and can improve liver tests and reduce cardiovascular morbidity in patients with mild to moderately abnormal liver tests that are potentially attributable to nonalcoholic fatty liver disease" (*Lancet* 2010;376:1916-1922). ■

Dosing timing for thyroxine

When is the best time to take thyroxine? Patients are generally told to take it on an empty stomach in the morning and wait at least 30 minutes before eating. A new study suggests that taking thyroxine at bedtime might be a better option. Over 6 months, 105 patients were randomized to take 1 capsule in the morning and 1 capsule at bedtime (one containing levothyroxine and the other a placebo), with a switch after 3 months. Taking levothyroxine at bedtime lowered thyrotropin levels and increased free thyroxine and total triiodothyronine levels (the primary outcome). Treatment did not change secondary outcomes including quality of life. The authors concluded that taking levothyroxine at bedtime is a good alternative to morning intake (*Arch Intern Med* 2010;170:1996-2003). This would likely benefit patients who find it difficult to wait 30 minutes to eat after taking their thyroxine each morning. ■

Rivaroxaban: an oral, factor Xa inhibitor

Rivaroxaban is an oral, direct factor Xa inhibitor that is approved in several countries for the prevention of venous thromboembolism (VTE) after orthopedic surgery. It is currently being evaluated by the FDA for this indication. Based on the findings of the EINSTEIN study, it appears the drug is also effective for the treatment of acute deep vein thrombosis (DVT). EINSTEIN consists of three randomized trials of rivaroxaban, one for the treatment of acute DVT, one for treatment of acute pulmo-

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nary embolism, and one for continued, long-term treatment in patients who have received treatment for acute DVT or pulmonary emboli. The results of the first and third wings of the study were recently reported in the *New England Journal of Medicine*.

In the DVT treatment arm, 3449 patients with acute DVT were randomized to rivaroxaban (50 mg twice daily for 3 weeks, followed by 20 mg once daily) or subcutaneous enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for 3, 6, or 12 months. In the continued treatment wing of the study, patients were randomized in a double-blind fashion to rivaroxaban 20 mg once daily or placebo for additional 6 or 12 months after completion of 6-12 months of treatment for VTE. The primary outcome for both studies was recurrent DVT. For the treatment of acute DVT, rivaroxaban was non-inferior to enoxaparin-vitamin K antagonist (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.44-1.04; $P < 0.001$). In the continued treatment study, rivaroxaban had superior efficacy compared to placebo (8 events [1.3%] vs 42 events [7.1%] with placebo; HR 0.18; 95% CI, 0.09-0.39; $P < 0.001$). There were four patients in the rivaroxaban group with non-fatal major bleeding vs none in the placebo group. The EINSTEIN authors concluded that "Rivaroxaban offers a simple, single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation" (*N Engl J Med* 2010;363:2499-2510).

Rivaroxaban is also being evaluated for the prevention of stroke in patients with nonvalvular atrial fibrillation based on the ROCKET AF study, which was presented at the American Heart Association meetings in November 2010. If approved, it will join the recently approved direct thrombin inhibitor dabigatran (Pradaxa®) for this indication. Both drugs have the advantage over warfarin of not requiring ongoing lab monitoring. ■

Echinacea and the common cold

The National Center for Complementary and Alternative Medicine (NCCAM), a division of NIH, has been in existence for nearly 20 years, much of the time under the intense scrutiny of the mainstream medical community. Despite NCCAM's attempts to verify the effectiveness of alternative healing practices, most if not all rigorously studied modalities have been shown to be ineffective. The benefit of another alternative staple, echinacea, is questioned with the publication of a NCCAM-sponsored study testing the benefit of the herbal remedy for treating the common cold. More than 700 patients in Wisconsin with new-onset common cold were assigned to one of four groups: no pills, placebo pills (blinded), echinacea pills (blinded), or echinacea pills (unblinded). The primary outcome was severity of the cold by self reporting with secondary outcomes of interleukin-8 levels and neutrophil counts from nasal washes. The comparison of the two blinded groups showed a trend toward benefit for the echinacea group (an average decrease in duration of cold of 7-10 hours out of 1 week; $P = 0.089$), but no difference in mean illness duration. There were no differences in the secondary outcomes. The authors concluded that the differences in illness duration and severity were not statistically significant with echinacea compared to placebo (*Ann Intern Med* 2010;153:769-777). ■

FDA Actions

The FDA is removing the breast cancer indication for bevacizumab (Avastin-Genentech). The somewhat unusual move was made after an FDA advisory panel suggested last summer that the drug did not provide a survival benefit for patients with breast cancer and at the same time caused serious side effects. The drug is still approved for treating cancer of the brain, colon, kidney, and lung.

The **FDA advisory panel is recommending approval for the first new diet pill in a decade. Orexigen Therapeutics' Contrave® is a combination of the antidepressant bupropion and the opioid antagonist naltrexone.** The drug was recommended for approval by a vote of 13-7, with some committee members voicing concern about potential side effects of the drug and recommending close post-marketing follow-up and studies to assess the risk of major cardiac events. The recommendation to approve the drug was based on studies that show an average weight loss 4.2% greater than placebo.

The **FDA has approved denosumab for the prevention of skeletal related events (fracture and bone pain) in patients with bone metastases from solid tumors.** The drug, which is given as a once monthly injection, was approved after a 6-month priority review. Denosumab is a monoclonal antibody to RANKL, a protein essential for the formation, function, and survival of osteoclasts. Denosumab in a lower-dose formulation was recently approved for the treatment of osteoporosis under the trade name Prolia™. Amgen Inc. will market the drug for this new indication under the trade name Xgeva™. It is expected to compete strongly with Novartis Pharmaceutical's zoledronic acid (Zometa®), which is approved for the same indication. ■