



SOP Newsletter

Drug Information News From the School of Pharmacy Faculty Members

January 2014; Vol 1, issue 4

January 2014;
Volume 1, issue 4

In this edition:

Topic in the news

- 2013 ACC/AHA Cholesterol guideline

Updates in

- **New drug of the month**
 - Eslicarbazepine
- **Drug approval**
 - Simeprevir
- **Psychiatric diseases**
 - Methylphenidate in ADHD
- **Pediatric disorders**
 - Sold food and allergy
- **Cardiology**
 - Metoprolol on infarct size
- **Vaccination**
 - Rotavirus and seizure
- **Biologic medical products**
 - Biosimilars
- **Women's health**
 - Maternal vit D
- **Bariatric surgery**
 - Drug considerations
- **Oncologic diseases**
 - Acute promyelocytic leukemia
- **Drug review**
 - Rosiglitazone

Patient corner

- Stem cells

ASHP poster

Announcements

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TOPIC IN THE NEWS

NEW GUIDELINES

2013 ACC/AHA guidelines to reduce atherosclerotic cardiovascular disease

Key point: The American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly issued four new guidelines that focus on the prevention of atherosclerotic cardiovascular disease (ASCVD). The guidelines discuss better risk assessment and management of cholesterol, lifestyle and weight.

Finer points: Both the ACC and the AHA aim to prevent CV disease and improve care of people living with or at risk of CV disease. The guidelines should help at achieving this, by providing guidance to various health care professionals (including primary care physicians, pharmacists, nurses and specialists) in how to best manage care, based on evidence up through 2011.

CV risk assessment

One of the guidelines introduces a new way to estimate a patient's risk of having an atherosclerotic CV disease event in the next 10 years, incorporating the patient's age, sex, total and HDL cholesterol, systolic blood pressure, blood pressure treatment, diabetes and smoking. In contrast to previous risk assessment tools, the new equation considers risk of stroke. It should help predict which patients will benefit most from interventions. Additional factors are discussed that may help to further define a patient's risk.

Modifying cholesterol levels

The guideline that deals with management of blood cholesterol levels no longer gives hard treatment targets for LDL cholesterol (LDL-C) and non-HDL cholesterol (non-HDL-C). Rather, it is recommended that an appropriate intensity of therapy is determined for a given patient, in order to reduce his or her risk in combination with a heart-healthy lifestyle. The guideline advises to give statin therapy irrespective of LDL cholesterol levels, thus frequent blood testing is no longer recommended.

Among all lipid-lowering therapies, statins show the strongest evidence for a favourable risk-benefit ratio. Four groups of patients are described that are considered to benefit the most from statin therapy:

1. Those with a history of CV disease,
2. Those with LDL-C >190 mg/dL,
3. Patients with diabetes aged 40-75 without a history of clinical atherosclerotic CV disease and LDL-C of 70-189 mg/dL,
4. Those with a 10-year CV risk according to the new equation but without a history of CV disease.

Based on the new guideline, the number of patients receiving statin therapy is expected to increase. The guideline recommends which groups should receive high-intensity statin therapy, or when moderate-intensity treatment may suffice, based on the new risk assessment equation.

Lifestyle management

The guideline on lifestyle management focuses on the importance of a healthy dietary pattern, which included many fruits, vegetables, whole grains, low-fat dairy, legumes, fish, poultry, and nuts, while sweets, sugar-sweetened beverages and red meats should be consumed with moderation. Evidence is provided that restricted intake of saturated fat and trans-fat can reduce cholesterol levels, and that sodium restriction can help reduce blood pressure.

40 minutes of moderate-to-vigorous physical activity on 3 to 4 days a week is recommended.

Management of overweight and obesity

The last new ACC/AHA guideline considers maintenance of a healthy weight, and was developed in collaboration with the Obesity Society. It is recommended to use body mass index as a quick first evaluation, to be complemented by a measurement of waist circumference, in order to determine risk of CV disease, diabetes and death.

Evidence is given that even modest weight loss of about 3-5% is associated with clinically meaningful benefits. No specific diet is recommended to achieve weight loss. Rather, recommendations to reduce caloric intake should be based on patient preferences and health status.

The guideline strongly advises at least 6 months of counseling on diet and exercise, or even comprehensive specialized programmes to lose weight.

Bariatric surgery is considered an appropriate option in patients with a BMI of >35 kg/m² and obesity-related comorbidities, or with BMI >40 kg/m² regardless of comorbidities.

What you need to know: The cardiovascular risk assessment guideline included a new sex- and race-specific method for calculating 10-year risk that replaces Framingham risk assessment. The lifestyle guideline and obesity guideline added specific diet, exercise, and weight loss recommendations. The guideline on the treatment of cholesterol explained that no evidence was found that supports the use of fixed LDL-C or non-HDL-C goals to guide therapy. Instead, the guideline identifies patient groups for whom moderate- or high-intensity statin therapy is recommended. These guidelines—which replace parts of the Adult Treatment Panel III, better known as ATP III, and the Obesity-1 guidelines—should be used to develop a comprehensive strategy for primary prevention of ASCVD.

Sources: 1. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Goff DC, Lloyd-Jones DM, Bennett G, et al., J Am Coll Cardiol. 2013.
 2. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Stone NJ, Robinson J, Lichtenstein AH, et al., J Am Coll Cardiol. 2013.
 3. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Eckel RH, Jakicic JM, Ard JD et al., J Am Coll Cardiol. 2013.
 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society Jensen MD, Ryan DH, Apovian CM, et al., J Am Coll Cardiol. 2013.

Razan Mhanna, PharmD.

NEW DRUG OF THE MONTH

Eslicarbazepine as add-on therapy for partial-onset seizures

Key point: The United States (US) Food and Drug Administration (FDA) approved eslicarbazepine acetate (Aptiom®), on November 2013, as an adjunctive therapy for partial-onset seizures associated with epilepsy in adults. The precise mechanism by which it exerts its anticonvulsant activity is thought to involve inhibition of voltage-gated sodium channels.

Finer points: Epilepsy is one of the most common neurological diseases and partial seizures are the most common type of seizure in people with epilepsy. The treatment of partial seizure presents a constant challenge; in fact, up to 58% of patients with partial-onset seizures do not achieve seizure control with current antiepileptic drugs.

Structurally, eslicarbazepine acetate (ESL) is a carboxamide that belongs to the dibenzazepine family and is closely related to carbamazepine and oxcarbazepine. Its main mechanism of action is by blocking the voltage-gated sodium channel, selectively in groups of rapid-activation neurons.

ESL is a pro-drug that is rapidly metabolized

“Eslicarbazepine has a better pharmacokinetic profile and tolerability than oxcarbazepine”

almost exclusively into S-licarbazepine, the biologically active drug. Compared to oxcarbamazepine, immediately after dosing it may not produce as high peak levels of (S)-(+)-licarbazepine. However, it may induce the metabolism of oral contraceptives and should be used with caution in females of child-bearing age.

The approval was based on 3 large phase III

trials including more than 1400 patients. The trials jointly showed statistically significant reductions (≥ 50% from baseline) in standardized seizure frequency vs. placebo (41% vs. 22%).

Treatment is started at 400 mg orally once daily and increased to 800 mg once daily (recommended maintenance dosage) after one week. Maximum recommended maintenance dosage is 1200 mg once daily. Patients with moderate to severe renal impairment will have 50% lower dose with a maximum recommended maintenance dosage of 600 mg once daily.

The most common reported adverse effects included dizziness, drowsiness, nausea, headache, double-vision, vomiting, fatigue, ataxia and loss of coordination. Like other antiepileptic drugs, eslicarbazepine may cause suicidal thoughts or actions. Hyponatremia has been observed (0.6%–1.3%), but the incidence appears to be lower than with oxcarbazepine. There is very limited information on the use of ESL in children or as monotherapy.

What you need to know: Eslicarbazepine acetate is a new anticonvulsant approved as a single-daily dose adjunct therapy for partial-onset seizures in epileptic adults. It is a sodium channel blocker similar to.

Source: 1. Dulsat C, et al. Eslicarbazepine acetate. Drugs Fut 2009; 34 (3): 189
 2. FDA approves Aptiom to treat seizures in adults. FDA News Release; November 8, 2013
 3. Mauri-Llerda JA. Eslicarbazepine acetate: a novel therapeutic alternative in the treatment of focal seizures. REV NEUROL 2012;54:551-555
 4. Serrano-Castro PJ, et al. Eslicarbazepine acetate in clinical practice. Efficacy and safety results. REV NEUROL 2013;56:309-314
 5. Rajinder P, et al. A Review of Eslicarbazepine Acetate for the Adjunctive Treatment of Partial-Onset Epilepsy. Journal of Central Nervous System Disease 2011;3 179–187

DRUG APPROVAL

Samar Younes, PharmD.

Approval of simeprevir for chronic hepatitis C virus infection

Key point: On November 22nd, 2013, the U.S. FDA approved simeprevir (Olysio™), a protease inhibitor, for the treatment of chronic hepatitis C infection. Simeprevir is part of an antiviral treatment regimen in combination with pegylated interferon and ribavirin in genotype 1 infected adults with compensated liver disease, including cirrhosis. It may benefit patients with chronic hepatitis C, including those who are treatment naive or who have failed prior interferon-based therapy.

Finer points: Simeprevir works by blocking the viral protease enzyme that enables the hepatitis C virus(HCV) to replicate in host cells. It is the third FDA-approved protease inhibitor to treat chronic hepatitis C virus infection after boceprevir and telaprevir previously approved in 2011.

The approval was based on efficacy and safety results from three pivotal Phase 3 studies – QUEST-1 and QUEST-2 in treatment-naive patients and PROMISE in patients who have relapsed after prior interferon-based treatment – as well as data from the Phase 2b ASPIRE study in prior non-responder patients. Each of the studies evaluated simeprevir dosed once daily in combination with pegylated interferon and ribavirin versus treatment with placebo plus pegylated interferon and ribavirin.

Results from a pooled analysis of QUEST-1 and QUEST-2 demonstrated that 80 percent of treatment-naive patients in the group receiving simeprevir achieved sustained virologic response 12 weeks after the end of treatment (SVR12), compared with 50 percent of patients in the placebo groups. In PROMISE, 79 percent of prior-relapser patients in the simeprevir group of the

study achieved SVR12 compared with 37 percent of patients in the placebo group. Results from ASPIRE demonstrated that use of simeprevir led to sustained virologic response 24 weeks after the end of treatment (SVR24) in 65 percent of prior partial-responder patients and 53 percent of prior-null responder patients compared with 9 percent and 19 percent of prior partial- and null-responder patients in the placebo groups, respectively.

“Simeprevir can benefit patients who are treatment naive or who have failed prior interferon-based therapy”

The most common side effects reported in clinical study participants were rash (including photosensitivity), itching (pruritis) and nausea. Serious photosensitivity reactions resulting in hospitalization were reported. Patients will be advised to limit sun exposure and to use sun protective measures during treatment with simeprevir in combination with peginterferon alfa and ribavirin. Simeprevir should not be used alone to treat chronic hepatitis C infection.

What you need to know: The FDA approval of simeprevir is an important milestone for people living with chronic hepatitis C as it means that patients have a new treatment option with the potential to cure this challenging disease.

Sources: 1. Janssen Therapeutics. OLYSIO (simeprevir) Receives FDA Approval for Combination Treatment of Chronic Hepatitis C. November 22, 2013.
 2. R Klein and K Struble. FDA Hepatitis Update -- Olysio (simeprevir) for the treatment of chronic hepatitis C in combination antiviral treatment. November 25, 2013.
 3. Food and Drug Administration. FDA Approves New Treatment for Hepatitis C Virus. November 22, 2013.
 4. Medivir. Simeprevir has been approved in the USA as a new treatment for hepatitis C. Press release. November 22, 2013.

PSYCHIATRIC DISEASES

Diana Malaeb, PharmD.

Methylphenidate in the treatment of attention deficit hyperactivity disorder

Key point: To establish the efficacy and safety of methylphenidate (MPH) treatment for attention deficit hyperactivity disorder (ADHD) in a group of children and young people with learning disability and severe epilepsy.

Finer points: A retrospective study was conducted, by systematically reviewing the case notes of all patients treated with methylphenidate (MPH) for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) ADHD at a specialist epilepsy center between 1998 and 2005. Treatment efficacy was ascertained using clinical global impressions (CGI) scores, and safety was indexed by instances of >25% increase in monthly seizure count within 3 months of starting MPH. Eighteen (18) patients were identified with refractory epilepsies (14 generalized, 4 focal), IQ <70, and ADHD. Male patients predominated (13:5) and ADHD was diagnosed at a median age of 11.5 years (range 6-18 years). With use of a combination of a behavioral management program and MPH 0.3-1 mg/kg/day, ADHD symptoms

improved in 61% of patients (11/18; type A intraclass correlation coefficient of CGI 0.85, 95% confidence interval [CI] 0.69-0.94). Daily MPH dose, epilepsy variables, and psychiatric comorbidity did not relate to treatment response across the sample. MPH adverse effects led to treatment cessation in three patients (dysphoria in two, anxiety in one). There was no statistical evidence for a deterioration of seizure control in this group with the use of MPH.

What you need to know: Methylphenidate with behavioral management was associated with benefit in the management of ADHD in more than half of a group of children with severe epilepsy and additional cognitive impairments. Eighteen percent had significant side effects but no attributable increase in seizures. Methylphenidate is useful in this group and is likely to be under employed.

Source: Fosi T, et al. Methylphenidate treatment of attention deficit hyperactivity disorder in young people with learning disability and difficult-to-treat epilepsy: Evidence of clinical benefit. Epilepsia. 2013 Oct 15.

PEDIATRIC DISORDERS

Mariam Dabbous, PharmD.

Earlier introduction of infants to solid food and relationship to food allergy

Key point: Continuing breast-feeding while introducing infants to solid foods, and waiting at least 17 weeks to introduce those solid foods, may lead to fewer food allergies in infants; according to a nested case-control within a cohort study of mothers of infants diagnosed with a food allergy by age 2 years.

Finer points: The study population came out of the Prevalence of Infant Food Allergy Study (PIFA), in which 1140 infants were recruited between 2006 and 2008 as part of the EuroVall project, which spanned 9 European countries. For this new study, researchers chose 41 infants (born

between January 2006 and October 2007) who had been diagnosed with a food allergy plus 2 age-matched control participants, whose birthdays were the closest matches to the index infants' birthdays, for each patient.

The researchers asked the mothers to record in daily diaries anything their children ate or drank during the first year of life. To decrease the burden, they did not require amounts, just food or drink consumed. Median age of the mothers was 33 years (range, 19 - 43 years), and median infant weight came to 3420 g (range, 2160 - 5060 g).

The good part about the study is that the diaries that the moms kept were prospective. Once they were diagnosed with allergies, they went back to look at what they were eating. It was less biased, as far as diary history.

Hen’s Egg and Eczema

The researchers found that the median age for detection of a food allergy was 56 weeks, with the most common allergy being hen’s egg (22 infants) and with 12 infants allergic to more than 1 food. The most common symptom was eczema, diagnosed by physicians in 12 infants, with vomiting being the second most common symptom.

Although 95% of mothers initiated breast-feeding and continued for a median of 20 weeks (range, 0 - 64 weeks), median duration of exclusive breast-feeding was 8 weeks (range, 1 - 26 weeks), and 50% of mothers exclusively breast-fed for a median of 9 weeks. For infants who were fed cow’s milk and breast milk (allergy group, n = 27; controls, n = 72), duration of concurrent feeding was 5.5 weeks for the allergy group and 9 weeks for control patients, with a statistically significant difference between the groups (P = .015).

The results showed a protective effect on food allergy development when cow’s milk protein, in whatever form, was given in the infant’s diet concurrently with breast milk, which may help develop oral tolerance because of its immunologic factors.

Solid Food Introduction

The researchers calculated the median age for solid food introduction as 20.3 weeks overall, with rice (primarily baby rice) introduced at 20 weeks, carrots at 21 weeks, and apples and bananas at 22 weeks. Most commonly introduced before aged 17 weeks was rice, in 20 infants. Apples, bananas, and pears were introduced before aged 17 weeks in 11, 8, and 8 infants, respectively.

Food-allergic infants started solid foods significantly earlier than control patients (P = .044). The primary foods for food-allergic infants were cow’s milk (P = .049) and peanut (P = .037). Control participants were introduced to solids first, between 12 and 16 weeks, but significantly more food-allergic infants were introduced to complementary foods at ≤16 weeks than control infants (35% vs 14%; P = .011).

What you need to know: The researchers conclude that health professionals can provide advice that is consistent by encouraging exclusive breastfeeding for as long as possible, followed by continued breastfeeding alongside the introduction of complementary foods to maximize the duration of concurrent breastfeeding and solid food introduction.

Source: Grimshaw KE, et al. Introduction of Complementary Foods and the Relationship to Food Allergy. *Pediatrics* 2013;132:1529–1538.

CARDIOVASCULAR DISEASES

Etwal BouRaad, PharmD.

Effect of metoprolol on infarct size when used with percutaneous coronary intervention

Key point: The literature examining the utility of beta blockers in the setting of acute coronary syndrome (ACS) to limit infarct size has produced conflicting results within and across treatment eras. The METOCARD-CNIC trial (Ibanez et al., 2013) was a multicenter, prospective, randomized, blind-endpoint study comparing early IV metoprolol (prior to reperfusion) to no metoprolol prior to reperfusion.

Finer points: Patients were eligible for enrollment if they presented with an anterior STEMI, if

their symptom duration was >30 min, and if reperfusion could be performed within 6 h of symptom onset. Exclusion criteria included Killip class III or IV, PR interval >240 ms, type II or III atrioventricular block, systolic blood pressure <120 mmHg, heart rate <60 bpm persistently, history of prior MI, or currently active beta blocker therapy. All other treatment was identical for the two groups, including a recommendation for thrombus aspiration and glycoprotein IIb/IIIa use as well as initiation of oral metoprolol tartrate

after revascularization, if not contraindicated. Patients without enzymatic evidence of infarction were excluded from analysis. MRI was performed 5–7 days after infarction in all other patients. Infarct size was quantified by delayed gadolinium enhancement at a core laboratory by blind observers.

“IV metoprolol may reduce infarct size in Killip class I/II patients”

A total of 220 patients (106 receiving metoprolol, 114 controls) were included in the analysis. Relative to controls, infarct size was significantly lower (25.6 ± 15.3 vs 32.0 ± 22.2 g; p = .012) in patients treated with IV metoprolol. This difference was greatest in patients with TIMI grade 0–1 flow prior to PCI; in this cohort, infarct size was 26.7 ± 15.0 g in patients treated with IV metoprolol, and 34.4 ± 20.0 g in controls (p = .0024). There was no evidence of a protective

effect in patients with pre-PCI TIMI grade 2–3 flow (p = .6). A similar pattern was observed in the peak creatine kinase (CK) level and area under the curve of CK release, as well as in left ventricular ejection fraction as assessed by MRI. There was no difference in adverse cardiac events between groups in the first 24 h. There was, however, a trend toward a higher rate of progression to Killip class III/IV in patients treated with metoprolol (7.9% vs 6.9%; no statistics provided).

What you need to know: The study suggests that in Killip class I/II patients presenting soon after onset of symptoms, IV metoprolol may reduce infarct size. The long-term clinical implications of this effect have yet to be characterized.

Source: 1. Ibanez B et al. Effect of early metoprolol on infarct size in ST-segment-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: The effect of metoprolol in cardioprotection during an acute myocardial infarction (METOCARD-CNIC) trial. *Circulation* 2013;128:1495.

VACCINATION

Fouad Sakr, PharmD.

Protective association between rotavirus vaccination and childhood seizures

Key point: A full course of rotavirus vaccine administered to infants may reduce the risk for rotavirus-related seizures by as much as 21% during the year after vaccination.

Finer points: The Division of Viral Diseases, Epidemiology Branch, Centers for Disease Control and Prevention (CDC), has conducted a retrospective analysis of children born after February 28, 2006, the date of US licensing of rotavirus vaccine, through November 2009. The study population for analysis consisted of 250,601 children, 186,502 of whom had been fully vaccinated against rotavirus and 64,099 of whom had not been vaccinated against rotavirus, with most ranging in age between 8 and 18 months.

The researchers observed a statistically significant effect of about an 18% reduction in first-time seizures and 21% reduction in all seizures (risk ratio [RR], 0.816 [95% confidence interval

(CI), 0.729 - 0.914] for first-time seizures; RR, 0.790 [95% CI, 0.714 - 0.875] for all seizures).

The most probable mechanism for this risk reduction is the vaccine’s protective effect on systemic rotavirus infection, including extraintestinal complications involving the central nervous system. The vaccine may also prevent rotavirus-related nitric oxide elevation in cerebrospinal fluid that causes neurotoxicity or calcium channel fluctuations that lead to neurotransmitter dysregulation.

Limitations of the study include lack of generalization to children vaccinated with rotavirus vaccine RV1, because more than 99% of the study children had RV5 vaccinations. Another factor limiting generalization is the fact that all study children were enrolled in managed care organizations (MCOs), and are not necessarily representative of all children population.

However, the study concludes that a full course of rotavirus vaccination is associated with statistically significant reductions in the risk of childhood seizures during the year following last rotavirus vaccination. This reduction in childhood seizures complements the well-documented vaccine-related benefit of preventing diarrhea hospitalizations.

What you need to know: Results such as these not only are interesting scientifically, but

provide yet another reason to strongly promote universal rotavirus immunization. In addition, the study provides as an opportunity to reflect on the fact that sometimes, unexpected effects of vaccination are beneficial and are a cause for positive outcomes, rather than the more commonly publicized concern for unexpected adverse effects.

Source: Payne DC, et al. Protective Association Between Rotavirus Vaccination and Childhood Seizures in the Year Following Vaccination in US Children. Clin Infect Dis 2013. Published online November 21

BIOLOGIC MEDICAL PRODUCTS

Katia Iskandar, PharmD, MSc.

Biosimilars: Implications for pharmacists

Key point: Biologicals are large proteins molecules manufactured via the manipulation of living organisms, the resulting purified bulk drug can vary from one production run to the next, and any modification in manufacturing steps can yield a different product. Biologicals are readily recognized by the immune system as a result of their size and complexity and can directly induce a range of immunologic responses. Because biologicals cannot be copied in the precise way a small molecule can be duplicated and the term biosimilar is used for these products

Finer points: According to the Biologics Price Competition and Innovation (BPCI) Act, a biosimilar is a product for which “a clinical study or studies” are sufficient “to demonstrate safety, purity, and potency for one or more appropriate conditions of use for which the referenced product is licensed.” However, the indications for which a biosimilar is approved do not necessarily include all of the licensed uses of the innovator reference product.

A primary concern regarding biosimilars is the potential for small differences in the manufacturing or formulation to affect the clinical profile of the innovator product, especially with regard to safety considerations. Concerns exist that biosimilar versions may be associated with unique adverse

events not seen with the innovator drug.

Although the formal biosimilars approval pathway is still under development in the United States, biosimilars are well established in other parts of the world, most notably the European Union (EU), which accounts for 80% of the global spending on these molecules.

“Concerns exist that biosimilar versions may be associated with unique adverse events not seen with the innovator drug”

This milieu of uncertainty surrounding biosimilars is further clouded by the availability of alternative biologicals marketed incorrectly as biosimilars in the developing world, where regulatory standards are less robust than those in Europe and those being developed in the United States.

Due to their complexity, biosimilars will require a greater investment of time and clinical resources in support of approval as compared with small-molecule generics, which are adopted for use in health systems with little or no formulary review. Therefore, discounts associated with biosimilars are expected to be only 20–30%, much less than the price decreases frequently seen with generic small-molecule drugs.

The need for a regulatory pathway for copies of biologicals was finally addressed in 2010, when the BPCI Act was signed into law. At the time of writing, an officially recognized biosimilar had not been approved in the United States.

On February 9, 2012, FDA published guidance concerning the biosimilar-approval pathway in the form of three draft documents, two of which respectively address scientific and quality considerations in demonstrating biosimilarity to an originator reference product and one of which provides answers to key questions applicants have posed regarding implementation of the BPCI Act. The February 2012 guidance did not address biosimilars naming or requirements to achieve an interchangeability approval.

What you need to know: Pharmacists should be cognizant that biological product regulation varies from country to country and only interchangeable biosimilars are substitutable by a pharmacist without the intervention of the prescriber. In the US, primary aims of state legislation include ensuring that pharmacists do not automatically substitute noninterchangeable biosimilars, that appropriate notification is given to prescribers when interchangeable biosimilars are substituted, and that pharmacists obtain patient consent for biosimilar substitution in some cases.

Source: De Lucio S, et al. Biosimilars: Implications for health-system pharmacists. American Journal of Health-System Pharmacy. 2013;70(22); 2004-2017

WOMEN’S HEALTH

Dalal Hammoudi, MSc.

Maternal serum levels of vitamin D and neurocognitive development in the offspring

Key point: Vitamin D levels in the general population have decreased considerably over the past decade, with reports of approximately one billion people worldwide estimated to be vitamin D deficient. Widespread sub-clinical vitamin D deficiency (serum 25-hydroxyvitamin D less than 20 ng/mL) is aggravated by long hours of work indoors and avoidance of sunshine with the purpose of reducing skin cancer. Individuals from Europe, the Middle East, China and Japan are at elevated risk; deficiency is more common in women than men (9.2% vs. 6.6%) and pregnancy is known to represent a particularly high-risk situation.

Finer points: During pregnancy, vitamin D is important for a multitude of aspects. First, it maintains pregnancy; the circulating concentration of maternal active vitamin D rises in the first trimester and doubles by the end of the third trimester. The early rise is believed to be necessary to enable immunological adaptation by the mother

that is required to maintain normal pregnancy, and these vitamin D induced immunological changes are thought to prevent miscarriage.

Second, and in terms of fetal health, vitamin D ensures fetal supply of calcium for development of bones including those of the skull and promotes normal fetal brain development. Vitamin D insufficiency has been associated with reduction in bone mineral content in the offspring, perinatal growth restriction, altered brain development and adult mental health. Evidence suggests that adequate vitamin D during early life may prevent certain diseases in the offspring such as Type 1 diabetes, allergy, lower respiratory tract infections, and asthma.

A recent study by Whitehouse et al determined long-term association between maternal serum levels of vitamin D and behavioral, emotional and language outcomes in the offspring. Serum 25-hydroxyvitamin D levels of 743 Australian

women were measured at 18 weeks of pregnancy, a gestational age representing a critical window of fetal neurodevelopment. Offspring behavior and language skills were measured by standard tests at 2, 5, 8, 10, 14, and 17 years of age. No significant association was observed between maternal serum levels of vitamin D and behavioral or emotional problems at any age. In contrast, there was significant association between maternal vitamin D insufficiency and language impairment at 5 and 10 years of age. The risk of having a child with clinically significant language difficulties was increased by twofold in women with vitamin D insufficiency during pregnancy, compared to those with normal levels of vitamin D.

What you need to know: Vitamin D is required to maintain pregnancy, for skeletal development, and to promote normal brain growth. Prenatal vitamin D supplementation may reduce the risk of developmental language difficulties among children.

Source: 1. Morales E, et al. Maternal vitamin D status in pregnancy and risk of lower respiratory tract infections, wheezing, and asthma in offspring. *Epidemiology*. 2012 Jan;23(1):64-71.
2. Sorensen IM, et al. Maternal serum levels of 25-hydroxy-vitamin D during pregnancy and risk of type 1 diabetes in the offspring. *Diabetes*. 2012 Jan;61(1):175-8
3. Morse NL. Benefits of docosahexaenoic acid, folic acid, vitamin D and iodine on foetal and infant brain development and function following maternal supplementation during pregnancy and lactation. *Nutrients*. 2012 Jul;4(7):799-840.
4. Whitehouse AJ, et al. Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. *Pediatrics*. 2012;129(3):485-93.

BARIATRIC SURGERY

Marwan Akel, PharmD.

Drug Consideration in Bariatric Surgery Patients (I)

Key point: The number of bariatric surgeries performed has increased dramatically. Bariatric procedures are generally either: gastric restriction to stimulate weight loss by limiting food intake and causing an early feeling of satiety or a hybrid of gastric restriction and induction of some type of malabsorption in the gastrointestinal tract.

“All patients should receive a multivitamin and calcium supplementation indefinitely”

Finer points: Nutrient deficiencies are less common in patients who have restrictive procedures compared to mal-absorptive ones. All patients should receive a multivitamin and calcium supplementation indefinitely. The partitioning of the stomach during bariatric surgery results in a dramatic decrease in the production of hydrochloric acid, affecting the absorption of calcium and iron. However, their absorption can be increased by using different salt forms or manipulating gastric pH: Calcium carbonate depends on acid for its absorption; calcium citrate does not. In other hands iron salts can be combined with ascorbic acid to acidify the stomach environment and facilitate its absorption. Concerning vitamin B12, its absorption is dependent on the presence of intrinsic factor, which is produced in the parietal cells of the stomach. In addition, hydrochloric acid is necessary to cleave vitamin B12 from protein so monthly B12

injections are effective in this population; however, appropriate supplementation can also be achieved by using the oral formulation (1000 µg daily).

During the immediate peri-operative period, obesity-related medical co-morbidities change dramatically, many chronic medical conditions improve postoperatively with weight loss, requiring close monitoring, and changing in the medications prescribed for those conditions.

Pharmacokinetic data characterizing the impact of various bariatric surgeries on drug absorption and metabolism are scarce; In patients who have had gastric bypass surgery, the small pouch located at the top of the stomach produces much less hydrochloric acid than the stomach previously did, possibly decreasing the absorption of medications dependent on acidic environments for solubility or absorption, and by bypassing major portions of the small intestine, Roux-en-Y bypass procedures drastically reduce the surface area for absorption.

What you need to know: These changes may warrant manipulation in drug route or dose to ensure adequate delivery.

Sources: 1. Anderson HF. Bariatric Surgery in Women: Medication Considerations; *US Pharm*. 2012; 37(9): HS-12-HS-16.
2: April D, et al. Medication and nutrient administration considerations after bariatric surgery; *Am J Health Syst Pharm* 2006 63: 1852-1857

Zain Al-Jamaly, PharmD.

ONCOLOGIC DISEASES

Advancements in the management of acute promyelocytic leukemia

Key point: Acute myeloid leukemia (AML) refers to a group of hematopoietic neoplasms involving cells committed to the myeloid lineage. Acute promyelocytic leukemia (APL) is a biologically and clinically distinct variant of AML. APL was classified as AML-M3 in the older French-American-British (FAB) classification system and is currently classified as acute promyelocytic leukemia with t(15;17) (q24.1;q21.1);PML-RARA in the WHO classification system.

Finer points: Without treatment, APL is the most malignant form of AML with a median survival of less than one month. However, with modern therapy, APL is associated with the highest proportion of patients who are presumably cured of their disease. The treatment of APL is distinct from that of other types of AML and is comprised of several stages which, in total, may span one to two years of treatment

- Remission induction
- Consolidation
- Maintenance

All-trans retinoic acid (ATRA) plus chemotherapy has been the standard induction therapy for patients with acute promyelocytic leukemia (APL). This combination is appeared to be synergistic that ATRA (a differentiating agent) is added to prevent the over differentiation that may occurs with ATRA alone (prevent the ATRA or differentiation syndrome), however there is always the risk of myelosuppression and cardiotoxicity with the use of these cytotoxic antibiotics.

Arsenic trioxide (ATO) has been used in practice for APL patients who are refractory to the standard AIDA regimen or patients who relapse after a successful induction, The Intergroup

“The off-label use of ATO plus ATRA is an acceptable alternative to ATRA plus chemotherapy for patients with low/intermediate-risk APL”

APL0406 randomized phase III trial compared ATRA plus arsenic trioxide with ATRA plus idarubicin (AIDA) in over 1500 adults with newly diagnosed low- or intermediate-risk APL (ie, with a total white blood cell count ≤10 x 10⁹/L)⁴. When compared with AIDA, ATRA plus ATO was associated with fewer deaths during induction therapy and similar rates of complete remission and rates of relapse at two years, resulting in a superior estimated event-free and overall survival at two years.

What you need to know: The off-label use of ATO plus ATRA is an acceptable alternative to ATRA plus chemotherapy for patients with low/intermediate-risk APL. A preference for this new regimen places a high value on the lesser myelosuppression and cardiac toxicity and less value on the longer clinical experience with ATRA plus chemotherapy. It is unknown whether these outcomes can be applied to higher risk disease.

Source: 1. Lo-Coco F, et al. ATRA and arsenic trioxide (ATO) versus ATRA and idarubicin (AIDA) for newly diagnosed, non-high risk acute promyelocytic leukemia (APL): Results of the phase III, prospective, randomized, intergroup APL0406 study led by the Italian-German cooperative groups GIMEMA-SAL-AMLSG. 2012 ASH Annual Meeting
2. Swerdlow SH, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, IARC Press, Lyon 2008.
3. Tallman MS, et al. Acute promyelocytic leukemia: evolving therapeutic strategies. *Blood* 2002; 99:759.
4. Hillestad LK. Acute promyelocytic leukemia. *Acta Med Scand* 1957; 159:189.

Good news for rosiglitazone?

Key point: In 2007, rosiglitazone was placed in the spot light after the results of a meta-analysis entitled “Effect of rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes” showed a 43% increased risk of heart attack from it.

Finer points: In response to these results, the U.S. FDA announced in 2010 that it would restrict the use of rosiglitazone to the following:

- Type 2 diabetic patients who were already taking the drug.
- Patients who could not control their diabetes on other medications.
- Only specially certified healthcare providers could prescribe it
- Only specially certified pharmacies could dispense it.

In addition, it instructed GlaxoSmithKline (rosiglitazone’s manufacturer) to direct an independent review of RECORD (rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes), the original trial that showed rosiglitazone as safe and effective.

At the same time, rosiglitazone was pulled from the European market. Its use started declining, in fact in 2013 rosiglitazone was being taken by only about 3,000 Americans, down from 120,000 before the restrictions were put in place.

In June 2013, the readjudicated results of RECORD conducted by the Duke Clinical Research Institute (DCRI) were reviewed by two FDA advisory panels. The results showed no elevated risk of heart attack or death in patients being treated with rosiglitazone when compared to standard-of-care diabetes drugs, contradicting what was reported in 2007.

On the basis of the recommendations from the expert advisory committees, the FDA announced in November 25th, 2013 that it is lifting restrictions on the prescribing and dispensing of rosiglitazone.

“ FDA announced that it is lifting restrictions on the prescribing and dispensing of rosiglitazone”

The FDA’s actions include:

- Modifications of rosiglitazone labeling about cardiovascular safety.
- Modifications in the handling of the drug: It will no longer require health care professionals, pharmacists, and patients to enroll in the rosiglitazone Risk Evaluation and Mitigation Strategy (REMS) program to prescribe, dispense, or receive rosiglitazone medicines.
- * Patients will again be able to receive the drug through regular retail pharmacies and mail order pharmacies.
- Required releasing a postmarketing study.

What you need to know: Once the changes are final, the FDA anticipates that the new indication for rosiglitazone will state that it may be used along with diet and exercise to improve glycemic control in type 2 diabetic patients, an indication similar to other currently available diabetes drugs. Will this grant a comeback for rosiglitazone in the diabetes world? Time will reveal all...

Sources: 1. Nissen SE, et al. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. N Engl J Med 2007; 356:2457-2471
 2. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm376516.htm>
 3. <http://www.fda.gov/Drugs/DrugSafety/ucm376389.htm>
 4. <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM143413.pdf>

What is regenerative medicine and stem cells?

Because people are still suffering from many devastating diseases in the world today, science strive to reach and benefit from the full power of stem cells to save lives and improve quality of life through regenerative medicine.

Regenerative medicine is the process of replacing or regenerating damaged tissues or organs in the body by using stem cells in order to stimulate the body’s own repair mechanisms to heal or restore previously irreparable tissue or organs.

Stem cells are cells that have the potential to differentiate into many different types of cells in the body. These cells have the capacity of self-renewal and can migrate to different organs for precise functions such as repair and renewal of damaged tissues.

These cells are found in the embryos (embryonic stem cells) and in adult tissues:

- Early stages of developing embryos
- Bone marrow
- Peripheral blood
- Fat
- Umbilical cord blood and tissue

Therapeutic uses of stem cells:

Nowadays, we have the opportunity to treat a number of health diseases and disorders by using such innovative technology such as:

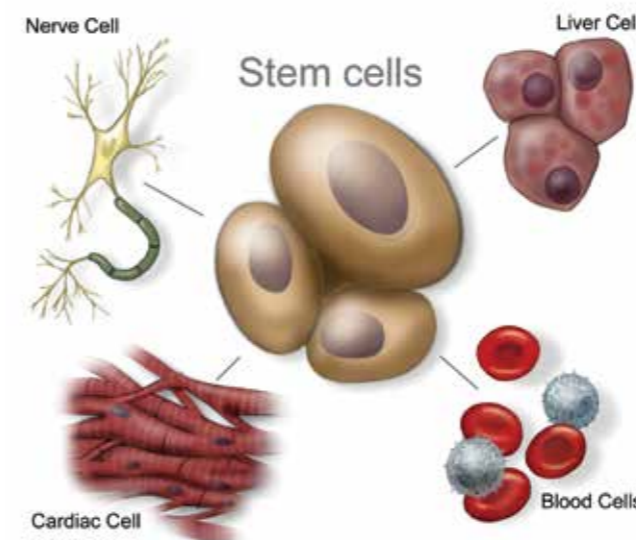
- Cardiovascular diseases (infarction, stroke)
- Metabolic diseases
- Diabetes
- Infertility
- Spinal cord injuries
- Cosmetic medicine (wrinkles, stretch marks, burns, wound, skin ulcers...)
- Ophthalmology problems...

How can you benefit from your baby’s umbilical cord blood?

Umbilical cord Blood, also known as placental blood, is the blood that circulates in the developing fetus and remains in the placenta and in the attached umbilical cord after childbirth. Umbilical cord blood is a rich source of stem cells that have the capacity to differentiate into a wide variety of different cell types.

Umbilical cord blood banking consists of long-term storage of stem cells collected from fetal blood that remains in the umbilical cord at the time of birth, by inserting a needle into the placental vein allowing the cord blood to flow by gravity into a sterile, anti- coagulating blood- collection bag. Then, immediate processing of the cord blood within 6 to 9 hours and quality controlled tests will be performed before and after the processing. The last step will be the storage (Banking) in liquid Nitrogen at – 196C for up to 25 years.

Source: Reviva Regenerative Medicine Center available online at <http://www.revivamedical.com/>



Evaluation of anticoagulation prophylaxis in patients hospitalized at a Lebanese medical center

Jihan Safwan, Pharm. D.; Katia Iskandar, Pharm. D., Marwan Akel, Pharm. D.

Introduction: Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major complication that is frequently encountered in medical and surgical practice. Appropriate VTE prophylaxis in inpatients is crucial to reduce the risk of post thrombotic complications and fatal and nonfatal PE. High risk VTE patients should be considered for evidence based anticoagulation, with: low molecular weight heparin (LMWH), unfractionated heparin (UH), fondaparinux, or vitamin K antagonist, unless contraindicated.

Objectives: Evaluate anticoagulation prophylaxis in patients hospitalized at a Lebanese medical center and increase awareness about the need to enhance knowledge

Methods: During the year of 2012, 122 patients from different hospital units including 83 males and 39 females. Their age ranged from 17 to 90 years old (mean 46.8 +/- 19.8). No contraindications to pharmacologic VTE prophylaxis were reported. This hospital follows the "Caprini model" to assess the eligibility of inpatients for VTE prophylaxis. A data collection sheet was filled to check the appropriateness of the practice of VTE prophylaxis and its adherence to the established guidelines

Results: Enoxaparin (Enox) was the LMWH of choice at this center. The "Caprini model" involves a risk assessment score, whereby a number of risk factors were attributed to 1, 2, 3, and 5 points based on their severity

Treatment was given according to the total risk score as follows: Thus: 52 patients (42.6%) received enoxaparin and 70 patients (57.4%) did not receive any drug therapy (Chi Square: P < 0.001).

Discussion: Concordance between Caprini's theory and practice revealed that: 28 (37.3%) eligible patients did not receive VTE prophylaxis and 5 (10.6%) non-eligible patients were on VTE prophylaxis (Cohen's Kappa = 0.48 +/- 0.07; p < 0.001; OR = 14.1 [5-39.8]). So, regardless of the presence of the Caprini risk assessment model at this medical center, errors are still encountered in the practice of VTE prophylaxis

Conclusion: According to Caprini's recommendation, "a careful individual assessment of thrombosis risk must be done in every patient to minimize the morbidity and mortality of venous thromboembolic events." Medical doctors and pharmacists should be encouraged to follow appropriate guidelines to ensure adequate prophylaxis against VTE.



Identify vitamin B12 risk factors and increase level awareness for chronic metformin users
 Amani Abbas, Pharm.D.; Etwal Bou Raad, Pharm.D.; Mohamad Iskandarani, MSc; Diana Malaeb, Pharm.D.
 Lebanese International University; Beirut, Lebanon

3-043

Background

Metformin a cornerstone in the treatment of type II Diabetes Mellitus (DM); associated with vitamin B12 malabsorption on long term treatment. Vitamin B12 important for many cellular process and its deficiency causes megaloblastic anemia & neuropathy. Unknown prevalence of vitamin B12 deficiency in Lebanon & its measurement is not part of the standard annual review examination

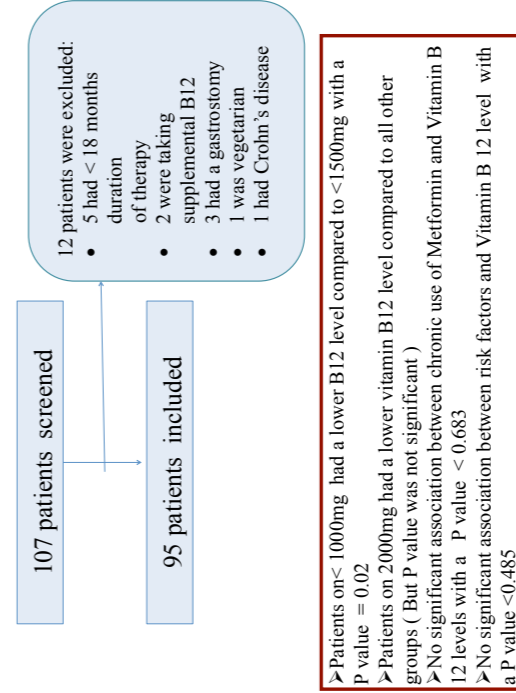
OBJECTIVES

Primary:
 - Screen diabetic patients on metformin for vitamin B12 level
 - Assess the role of pharmacists in collaboration with MDs to increase patient awareness about the disease & its treatment
Secondary:
 - Evaluate the association between metformin dose, & duration of therapy with vitamin B12 deficiency
 - Evaluate other risk factors associated with vitamin B12 deficiency

METHODS

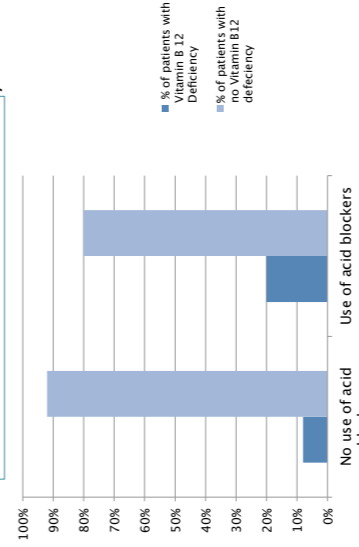
Prospective multicenter descriptive study in a hospital & in different clinics from December 2012 to May 2013
Inclusion criteria:
 - Type II DM on metformin for ≥ 18 months
Exclusion criteria:
 - History of pernicious anemia, vegetarian
 - Metformin treatment < 18 months
 - Chronic renal insufficiency defined by a creatinine > 1.5
 - Previous surgical history that affects vitamin B12 absorption
 - Pregnancy, tumors, inflammatory bowel disease & psoriasis
 - Vitamin B12 supplementation in the previous 3 months
Procedure:
 - Patients records retrieved for demographic information
 - Primary questionnaire filled by patients then counseled by PharmD candidate on diabetes, metformin & vitamin B12 role
 - Same scores were used before & after counseling to assess patient awareness
Statistical Analysis:
 - Associations between categorical values and B12 deficiency were done with ANOVA test
 - Associations between use acid blockers and Vitamin B12 levels were done with Pearson Chi Square test

RESULTS

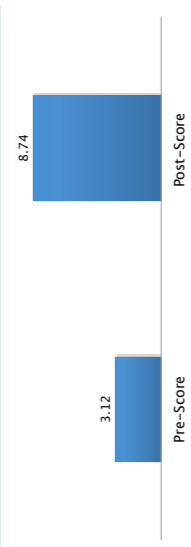


DISCUSSION

Acid blockers and Vitamin B12 deficiency



Awareness result score before and after counseling

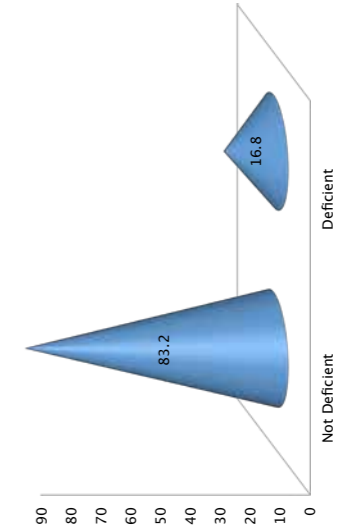


CONCLUSION

Finding a prevalence of 16.8% raises the question of whether to screen for B12 deficiency in all patients receiving metformin
 Clinical pharmacists play an important role in raising awareness among patients regarding on diabetes, metformin and vitamin B12 deficiency & thereby improve overall clinical outcomes

DISCLOSURE PANEL

The authors have nothing to disclose.



ANNOUNCEMENTS

EVENTS

The faculty members of the school of pharmacy:

- Organized and attended 8th annual dinner for the graduates of the class for the academic year 2012-2013 at the Coral Beach Hotel and resort in Beirut. The prestigious dinner was hosted under the patronage of H.E. Mr. Abdel Rahim Mourad. It was attended by Dr. Bahij Arbid , the representative of the Minister of Health, Mr. AbdelMawla Chehab Eldine, Dr. Jamal Arafat, and Mr. Nazih Jebawi from the Ministry of Education and Higher Education, Mr. Rabih Hassouneh, the president of the Order of Pharmacists in Lebanon, OPL members, LIU administration and deans, faculty members, and graduates.
- Including Dr. Jihan Safwan and Dr. Faraj Saade attended the 2013 ASHP Midyear Meeting and Exhibition in sunny Orlando, Florida during the month of December 2013 from the 8th till the 12th in Orange County Convention center.
- Organized and attended the annual Christmas dinner on Thursday the 19th of December at Leila Verdun restaurant
- Organized and attended a series of seminars:
 - ◇ Breast cancer awareness: early detection saves lives presented by Dr. Hiba Jabaly
 - * On Tuesday the 5th of November, 2013 at Beirut campus
 - * On Wednesday the 18th of December 2013 at Bekaa campus
 - ◇ Stems cells banking and therapy application presented by Dr. Norman Makdissy and Ms. Sandy Hajj representative of Reviva Regenerative Medicine Center
 - * On Thursday the 28th of November, 2013 at Beirut campus
 - ◇ Anti-smoking campaign: towards a smoke free campus presented by Dr. Jamil Halabi president of the anti smoking task force
 - * On Thursday the 19th of December, 2013 at Beirut campus
 - ◇ Updates in vaccination presented by Dr. Rima Halat
 - * On Wednesday the 15th of January, 2014 at Bekaa campus
- Organized a site visit to Beesline industry for the first professional year students, on Friday the 3rd of January, 2014
- Organized a site visit to Deir Al Salib: “Hopital de la Croix” for pharmacotherapeutic I (neurology/psychiatry) students on Thursday the 16th of January, 2014

LIU social media

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The Scope

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