**Clinical Therapeutics**

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**Introduction:** Mirtazapine is a noradrenergic and serotonergic antidepressant mainly acting through blockade of presynaptic alpha-2 receptors. Published data on pregnancy outcome after exposure to mirtazapine are scarce. This study addresses the risk associated with exposure to mirtazapine during pregnancy.

**Patients (or Materials) and Methods:** Multicenter (n = 11), observational prospective cohort study comparing pregnancy outcomes after exposure to mirtazapine with 2 matched control groups: exposure to any selective serotonin reuptake inhibitor (SSRI) as a disease-matched control group, and general controls with no exposure to medication known to be teratogenic or to any antidepressant. Data were collected by members of the European Network of Teratology Information Services (ENTIS) during individual risk counseling between 1995 and 2011. Standardized procedures for data collection were used in each center.

**Results:** A total of 357 pregnant women exposed to mirtazapine at any time during pregnancy were included in the study and compared with 357 pregnancies from each control group. The rate of major birth defects between the mirtazapine and the SSRI group did not differ significantly (4.5% vs 4.2%; unadjusted odds ratio, 1.1; 95% confidence interval, 0.5–2.3, P = 0.9). A trend toward a higher rate of birth defects in the mirtazapine group compared with general controls did not reach statistical significance (4.2% vs 1.9%; OR, 2.4; 95% CI, 0.9–6.3; P = 0.08). The crude rate of spontaneous abortions did not differ significantly between the mirtazapine, the SSRI, and the general control groups (9.5% vs 10.4% vs 8.4%; P = 0.67), neither did the rate of deliveries resulting in live births (79.6% vs 84.3% in both control groups; P = 0.15). However, a higher rate of elective pregnancy-termination was observed in the mirtazapine group compared with SSRI and general controls (7.8% vs 3.4% vs 5.6%; P = 0.03). Premature birth (<37 weeks) (10.6% vs 10.1% vs 7.5%; P = 0.38), gestational age at birth (median, 39 weeks; interquartile range [IQR], 38–40 in all groups; P = 0.29), and birth weight (median, 3320 g; IQR, 2979–3636 vs 3230 g; IQR, 2910–3629 vs 3338 g; IQR, 2967–3650; P = 0.34) did not differ significantly between the groups.

**Conclusion:** This study did not observe a statistically significant difference in the rate of major birth defects between mirtazapine, SSRI-exposed, and nonexposed pregnancies. A slightly higher rate of elective pregnancy-termination was observed in the mirtazapine group compared with SSRI and general controls (7.8% vs 3.4% vs 5.6%; P = 0.03). Premature birth (<37 weeks) (10.6% vs 10.1% vs 7.5%; P = 0.38), gestational age at birth (median, 39 weeks; interquartile range [IQR], 38–40 in all groups; P = 0.29), and birth weight (median, 3320 g; IQR, 2979–3636 vs 3230 g; IQR, 2910–3629 vs 3338 g; IQR, 2967–3650; P = 0.34) did not differ significantly between the groups.

**Disclosure of Interest:** None declared.

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**OC004—FETAL EXPOSURE TO NONSTERoidal ANTiINFLAMMATORY DRUGS (NSAID) AND SPONTANEOUS ABORTIONS**

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**Introduction:** Spontaneous abortions are the most common complication of pregnancy and nonsteroidal anti-inflammatory drugs (NSAID) are among the most widely used groups of drugs during the first trimester of pregnancy. Published data are inconsistent regarding the risk for spontaneous abortions after exposure to NSAID.

**Patients (or Materials) and Methods:** A population-based retrospective cohort study was conducted including all women who conceived between January 2003 and December 2009 and admitted for birth or diagnosed with spontaneous abortion at Soroka Medical Center, Clalit Health Services, Israel. A computerized database of medication dispensation was linked with 2 computerized databases containing information on births and spontaneous abortions. Time-varying COX regression models were constructed adjusting for mother’s age, diabetes mellitus, hypothyroidism, hypercoagulable or inflammatory conditions, history of recurrent miscarriages, presence of intrauterine contraceptive device, ethnicity, and self-reporting tobacco use during pregnancy and the year of pregnancy.

**Results:** There were 65,457 women who conceived during the study period and admitted at SMC: 58,949 (90.1%) for birth and 6508 (9.9%) for spontaneous abortion. A total of 4495 (6.9%) pregnant women were exposed to NSAID during the study period. Exposure to NSAID was not an independent risk factor for spontaneous abortion as groups (adjusted hazard ratio [HR], 1.08; 95% confidence interval [CI], 0.97–1.20 and adjusted HR, 1.67; 95% CI 0.95–2.95 for nonselective and selective COX2 inhibitors, respectively) or as specific drugs. Additionally, no dose response effect was found.

**Conclusion:** In this large population-based retrospective cohort study, no increased risk for spontaneous abortions was found following exposure to NSAID Table.

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**Disclosure of Interest:** None declared.

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**OC005—BIASES ON THE ADMINISTERED PARENTERAL DOSES OF AN EXPERIMENTAL DRUG DURING PHASE I CLINICAL TRIALS**

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**Introduction:** The pharmaceutical aspects of drug administration in clinical trials receive poor consideration compared with the important attention devoted to the analytical and mathematical aspects
of biological sample exploitation. During PK calculations, many researchers merely use for dose the nominal amount declared, overlooking the noticeable biases that may result in the assessment of PK parameters. The aim of this work was to evaluate the biases related to doses injected of a biosimilar drug in 2 Phase I clinical trials.

Patients (or Materials) and Methods: In trial A, 12 healthy volunteers received different doses of a biosimilar of interferon beta-1a by either subcutaneous (SC) or intravenous (IV) injection. The doses were prepared by partially emptying 0.5-mL syringes supplied by the manufacturer (drop count procedure). In trial B, 12 healthy volunteers received 3 different formulations of the drug by IV injection (biosimilar without albumin [HSA], biosimilar with HSA and original brand [Rebif®]) and 2 different formulations as multiple SC injections (biosimilar HSA-free and original brand). In both trials, the actual dose administered was calculated as: D = C·V – losses. The product titer C was assessed by ELISA. The volume administered IV was assessed by weighing. Losses were evaluated by in vitro experiments. Finally, the binding of 125I-interferon to HSA was evaluated by counting the free and HSA complexed molecule fractions separated by gel filtration.

Results: Interferon was not significantly adsorbed onto the lines used for its IV administration. In trial A, the titer was very close to the one declared (96 ± 7%). In trial B, it differed significantly (156 ± 10% for biosimilar with/without HSA and 123 ± 5% for original formulation). In trial A, the dose actually administered showed a large variability. The real injected volume could be biased up to 75% compared with the theoretical volume (for the lower dose administered [i.e., 0.03 mL]). This was mainly attributed to a partial re-aspiration of the drug solution before withdrawing the syringe needle. A strict procedure was therefore applied in trial B to avoid these inaccuracies. Finally, in trial B, 125I-interferon beta-1a binding to HSA appeared time dependent and slow, reaching 50% after 16-hour incubation, which is close to steady state reported for the comparator Rebif®.

Conclusion: These practical examples (especially biases on actual titer and volume injected) illustrate that actual dose assessment deserves attention to ensure accuracy for estimates of clearance and distribution volume in the scientific literature and for registration purposes, especially for bioequivalence studies.


OC006—CRITICAL REVIEW OF THE VALIDATION PROCESS OF SIX PREDICTIVE BIOMARKERS: HOW GOOD IS THE QUALITY AND QUANTITY OF THE EVIDENCE?

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Introduction: Increasing efforts have been made on the research of new predictive biomarkers in drug development, particularly in oncology. In this context, the validation process represents a difficult task with some potential methodologic limitations. In the present study, we will perform a critical review of the validation process of 6 key biomarkers in oncology.

Patients (or Materials) and Methods: Six biomarkers were selected considering their relevance in drug development over the last decade in oncology: HER-2, EGFR, KRAS, C-KIT ALK, and C-Met. A review of literature was performed in PubMed, Cochrane, and EMBASE, and in regulatory agencies public websites. A critical review of available data in relation to regulatory requirements (EMA and FDA) has been conducted considering the following elements: at which stage of drug development the biomarker was considered in defining the target population; type of clinical data used for the biomarker validation process; impact of the biomarker in the final labeling; and availability of a standardized test applicable in clinical practice.

Results: Results are displayed according to recommendations of regulatory agencies on the necessary procedural steps for the validation process preapproval.

<table>
<thead>
<tr>
<th>Triggering Facts</th>
<th>Labeling Implications</th>
<th>Standardized Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER-2</td>
<td>Biomarker-based drug development</td>
<td>Restricted labeling to HER2 overexpression or HER2 gene amplification</td>
</tr>
<tr>
<td>EGFR</td>
<td>Failed studies in NSCLC</td>
<td>Unrestricted labeling in US</td>
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<td></td>
<td></td>
<td>Negative opinion in EU</td>
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<tr>
<td>KRAS</td>
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<td></td>
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<td>Negative opinion in US</td>
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<td></td>
<td></td>
<td>KRASwt at a later stage once prospectively validated</td>
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<tr>
<td>C-KIT</td>
<td>Exploratory analyses through the different indications</td>
<td>Not reflected in labeling</td>
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<tr>
<td>ALK</td>
<td>Biomarker-based drug development</td>
<td>Restricted labeling to anaplastic lymphoma kinase (ALK)-positive in NSCLC</td>
</tr>
<tr>
<td>C-Met</td>
<td>Biomarker-based drug development</td>
<td>Not reflected yet</td>
</tr>
</tbody>
</table>

Conclusion: Data analyzed allow to distinguish 2 different scenarios. Those situations in which the biomarker development was the consequence of a primarily failing drug development strategy (EGFR and KRAS) and those in which the biomarker was a key element prospectively considered in drug development (ALK, HER2, C-KIT and C-met). Regulatory decisions were adopted sometimes based on purely retrospective strategies. The authors will critically describe such circumstances and the potential clinical implications of such decisions.

Disclosure of Interest: None declared.

OC007—ASSESSMENT OF CLINICAL PHARMACOLOGY SKILLS AS PART OF THE NEW INTEGRATED FINAL EXAM FOR MEDICAL STUDENTS AT KAROLINSKA INSTITUTET

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Introduction: An integrated final exam for medical students was introduced at Karolinska Institutet, Stockholm, Sweden, in 2012. The exam is scenario based and consists of six 20-minute stations, 1 of which has been designed to assess clinical pharmacology (CP) skills. The overall aim of the exam is to assess the knowledge (both