Post-hoc analysis of gender effect on therapy: the METAGEM italian example

Mihaela Nica, Value&Access Manager
Berlin, November 6, 2015
Topics

- Clinical relevance of Gender Medicine
- The METAGEM project
  - Research question and methods
  - The GENDER ATTENTION study
  - Main poster communications and scientific publications
Drug usage in women is about 40% higher than in men
(F. Franconi, S. Montilla e S. Vella, Farmacologia di genere. 2010)

Antihypertensive drugs such as calcium antagonists appear to be more effective in women in terms of blood pressure reduction; on the other hand, ACE inhibitors seem to be able to diminish mortality in men but not in women.

Regarding depression treatments, women respond better to selective serotonin reuptake inhibitors, whilst men gain more benefit from tricyclic antidepressants.
(D.M. Sloan, S.G. Kornstein, Gender Differences in Depression and Response to Antidepressant Treatment. Psychiatric Clinical North America, 2003)
It has been proven that **women need to take higher doses of GH receptors antagonists** in order to reach the analogous effect in men to treat acromegaly.

*(Parkinson C et al. Gender, Body Weight, Disease Activity, and Previous Radiotherapy Influence the Response to Pegvisomant. The Journal of Clinical Endocrinology & Metabolism 92(1):190–195)*

**Ibutilide**, a class III antiarrhythmic agent, shows a **different efficacy profile** in men and women, and among women themselves during menstrual cycle progression.

*(Rodriguez I et al. Drug-Induced QT Prolongation in Women During the Menstrual Cycle. JAMA. 2001)*

**Women are more subjected to be resistant to aspirin** or to be partially respondent when it comes to myocardial infarction prevention.

Historically, **clinical research has been done especially in men**, generating biological and disease models inadequate for women, if not modified (Dr. Marianne Legato, director of the new Partnership for Women's Health at Columbia).

The lack of specific studies on women, especially in early phase research, determines two important consequences:

- does not allow to **measure drug real efficacy according to genders**
- may limit the **discovery of women-specific drugs**

(www.medicinadigenere.org)

Women disadvantages in clinical trials are abundant especially in testing drugs for diseases **not specifically or traditionally female**

(La sperimentazione farmacologica sulle donne, Comitato Nazionale per la Bioetica)
Things are moving though! Actions are taken
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  - Main results from expositions and scientific publications
The METAGEM project

Research question

The METAGEM project is aimed at evaluating gender differences in clinical outcomes, therapeutic approaches and safety parameters in Italian patients.
The METAGEM project
Methods – Studies included

Nine observational studies sponsored by Novartis and conducted in Italy between 2002 and 2013 in a range of different clinical areas were included in the project and analyzed from a sex-gender prospective.
The METAGEM project

Methods – Studies by pathological area

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<th>Studies/Projects</th>
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<td>PSYCHAE: Survey for the Control of Anxiety and Depression</td>
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<td>GENDER ATTENTION: Effetto del genere e dell’aspetto ormonale sull’incidenza di effetti collaterali in pazienti affetti da psoriasi a placche trattati con ciclosporina</td>
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<td><strong>Rheumatology (psoriatic arthritis)</strong></td>
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<td><strong>Transplants</strong></td>
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<td>CETRA: Complications related to gastrointestinal symptoms in renal transplant patients</td>
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The METAGEM project

Methods – Studies by design

Cross-sectional

Cross-sectional

Longitudinal up to 6-month follow up

Longitudinal 9-month follow up

Longitudinal 36-month follow up

Longitudinal 12-month follow up

Longitudinal 6-month follow up

Longitudinal 12-month follow up

Longitudinal 12-month follow up
Two analysis approaches were applied:

- **Post-hoc subgroup analysis** in which the groups of male and female patients were considered
- **Meta-analysis** of data of interest
The METAGEM project

Methods – Analysis approach: post-hoc subgroup analysis

- In all the studies, patients were assigned to **male and female groups** based on information provided by the clinicians in the sex field on the case-report forms.

- The groups of male and female patients were **compared by statistical tests** for:
  
  - Study-specific disease-related outcomes (e.g. disease severity, anamnesis)
  - Primary outcome(s) of the study
  - Therapies: prescribed/administered
  - Standardized scales, where applicable
  - Adverse events

*As post hoc analyses, all p-values presented were exploratory.*
Individual participant data (IPD) were meta-analyzed by means of a model that directly synthesizes the IPD in a one-step approach while accounting for the clustering of participants within studies.

The meta-analysis of IPD is an increasingly popular alternative to traditional methods for meta-analysis (which usually synthesize aggregate study-level data obtained from study publications or study authors) offering both statistical and clinical advantages.
The METAGEM project

Summary of analyses

**GENDER ATTENTION Study**

2010-2013

**Post-hoc analyses**

2013-2015

**Meta-analysis on safety**

All the above mentioned studies (except SURF) 2015
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The GENDER ATTENTION study aims to investigate, within the Italian clinical practice, the influence of gender and menopausal status on the incidence of adverse events in patients suffering from plaque psoriasis treated with cyclosporine.
The GENDER ATTENTION Study

*Impact on Media*

**Avviato studio italiano di genere su cure psoriasi**

*Promosso da Novartis, risultati a inizio 2013*

Valutare l'influenza del genere sulla differente incidenza di effetti collaterali in persone colpite da psoriasi e in trattamento farmacologico, come da pratica clinica, con ciclosporina. E questo l’obiettivo di “Gender attention”, il primo studio osservazionale italiano di medicina di genere promosso da un’industria farmaceutica, la Novartis, avviato da pochissimi mesi a Roma in occasione del “Gennaio della differenza”, promosso da Gennareg e dall’associazione salute e genere (Gneg) insieme a Novartis. “Lo studio - spiega Gabriele Rizzo, direttore medico di Novartis Farmaceutica - è un’indagine di base e di campionamento italiano organizzato specificamente per valutare la medicina della differenza. E’ partito nel maggio 2011 e coinvolge 52 centri e ambulatori da dermatologia convenzionali con il 55%. Lo studio coinvolge 800 donne e 400 uomini, in soli 7 settimane c'è stato il 180% di adesione. Abbiamo bisogno di un tempo ragionevole per completare lo studio - prosegue Rizzo - eppure le previsioni sono che la differenza esista realmente e che questo studio possa dare una risposta alla domanda di quel perché le donne e i fumi non reagiscono come dovrebbero nei confronti delle terapie per la psoriasi. L’obiettivo finale è che la medicina della differenza diventi in futuro un tema di interesse più ampio e più ampio in tutti i settori della medicina, non solo in dermatologia.”
Four patient cohorts were defined:

Fertile women (FW) and menopausal women (MW):
Defined based on clinician’s opinion
(menopause defined as absence of menstrual cycle for at least 12 months,

Men matched to FW and men matched to MW:
For each age class (30-34, 35-44, 45-54, 55+)
the proportion of FW and MW was computed
and an equal proportion of men was randomly selected.

Among 889 evaluable patients with plaque
psoriasis treated with cyclosporine:

336 fertile women matched with 253 men
182 menopausal women matched with 118 men
The GENDER ATTENTION Study

Main results – Adverse event incidence rate ratio

- Adverse event incidence rate is **37% higher** in fertile women than in matched men, and it is **18% higher** in menopausal women than in the matched men (differences are not statistically significant).

- Adverse event incidence rate in fertile women is about **33% lower** than in menopausal women (significant difference). This result is still significant even after adjusting for age.
The final results of the GENDER ATTENTION study confirm the **good safety profile of cyclosporine** in a large sample of Italian psoriatic patients.

The % of patients that experienced at least one AE was **higher in menopausal women than in fertile ones** (significant result).

Differences in the % of patients that experienced at least one AE between fertile women and matched men and between menopausal women and matched men were not significant.

AE incidence rate **was higher in menopausal women than in fertile ones** (significant result).

Differences in the AE incidence rate between fertile women vs. matched men and between menopausal women vs. matched man were not significant.
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The METAGEM project
Research posters

- 3 methodological posters presented at:
  - OSSD 2014 Meeting
  - ISPOR 17th Annual European Congress 2014
  - 90° SIDeMaST National Congress

- Poster on SYNERGY at 2015 7th IGM Congress.
The METAGEM project

Scientific publications

- 4 published paper
  - 1 (methodological)
  - 1 (Parkinson’s disease)
  - 2 (Dermatology - psoriasis)
- 1 paper (meta-analysis on safety) submitted
- 2 reviews: “Gender and pharmacoeconomics” and “Gender and nervous system” are in progress
A gender-medicine post hoc analysis (MetaGeM) project to test sex differences in previous observational studies in different diseases: methodology

Abstract: Only recently has medical research begun to understand the importance of taking sex into account, recognizing that symptoms and responses to medical treatment may be very different between males and females. However, the analyses provided by the pharmaceutical industry to regulatory authorities often do not present safety and efficacy data by sex. Novartis has started a gender-medicine project called MetaGeM, which includes nine observational studies sponsored by Novartis Farma, Italy, conducted in Italy between 2002 and 2013 in a range of different clinical areas. The MetaGeM project aims to analyze and describe by means of post hoc analyses and meta-analyses, clinical outcomes, therapeutic approaches, and safety data of these studies, by sex: PSYCHAE; GENDER ATTENTION in psoriasis; Synergy in psoriatic arthritis; ICEBERG in HBsAg carriers; SURF and CETRA in liver- and renal transplanted patients, respectively; DEEP in Parkinson’s disease; and EVOLUTION and AXEPT in Alzheimer’s disease. The present paper describes the methodology of the MetaGeM project.

Keywords: gender-medicine, MetaGeM project, methodology
617 patients, 62% males.

Wearing-off symptoms are more common among women, both for motor and non-motor symptoms:

- Prevalence of WO was higher among women (72.5% vs. 64%)
- Women experienced motor symptoms in 72.5% vs. 64% in men
- Women experienced nonmotor symptom in 44.5% vs. 37% in men
786 patients, 61% males.

Italian dermatologists seemed to have the same approach in treating male and female patients with psoriasis, although females should have deserved more attention to their higher psychological distress.
Prevalence of acute and chronic viral seropositivity and characteristics of disease in patients with psoriatic arthritis treated with cyclosporine: a post-hoc analysis of the SYNERGY study from a gender point of view

Delia Colombo, Sergio Chimenti, Paolo Grossi, Antonio Marchesoni, Federico Bardazzi, Fabio Ajala, Germana Camplone, Lucia Simoni, Donatalla Vassellatti, Gilberto Bellia on behalf of SYNERGY Study Group

Submitted to European Journal of Medical Research (BioMedCentral).

- 225 patients, 54% males.
- Women with psoriatic arthritis have a greater articular involvement and a higher activity of disease compared to males. Immunosuppressive treatment with cyclosporine seems not to increase susceptibility to new infections or infectious reactivations, with no gender differences.
The METAGEM project

Paper on the meta-analysis on safety

Gender differences in the adverse events’ profile registered in seven observational studies of a wide gender-medicine (MetaGeM) project: the MetaGeM safety analysis

Delia Colombo, Emanuela Zagni, Mihaela Nica, Sara Rizzoli, Alessandra Ori, Gilberto Bellia

Submitted to Drug Design, Development and Therapy (Dovepress).

- A meta-analysis of seven MetaGeM studies, aimed at evaluating possible gender differences in the incidence and severity of AEs.

- 4870 patients, 46% females and 54% males.

- There was no significant gender difference in the percentage of patients with at least one AE. Total SAEs were 47 (72% in men). The frequency of patients with ≥1 SAE was 0.6% in women vs 1.2% in men (χ2 test p-value = 0.0246).

- This safety analysis, on a large sample of almost 5000 patients affected with different diseases and treated with a wide range of different drugs, provides a useful overview on possible gender differences in drug tolerability, which may be helpful in more accurately designing future clinical trials in a gender-specific perspective.
Despite the limitations of retrospective non predefined analyses and of considering clinical data that are not always up to date, the MetaGeM project may lead to useful considerations on possible sex differences in a large spectrum of:
- **therapeutic approaches**
- **clinical response**
- **safety** of some diseases, in order to more appropriately design further clinical trials from a **sex-gender specific perspective**.
Thanks for your attention!