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

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Background: MetaGeM is a wide gender-medicine project comprising post hoc and meta-analyses by gender of clinical outcomes, therapeutic approaches, and safety data from previously conducted observational studies to explore possible gender differences in real-life clinical settings. We report the results of the safety meta-analysis of seven MetaGeM studies, evaluating gender differences in adverse event (AE) incidence and severity.

Methods: Data were collected between February 2002 and July 2013. Male and female patients were compared for the main safety variables, using Student's *t*-test, χ^2 test, or Fisher's exact test as appropriate. As supportive analysis, a logistic regression model was estimated to evaluate associations between gender and outcome.

Results: In total, 4,870 patients (46% females, 54% males) were included in the analysis; age was higher for females (mean ± standard deviation 61.2±18.3 years) than males (56.3±16.6 years). Overall, 264 AEs were reported (59.1% in males). There were no significant gender differences in the percentage of patients with at least one AE: 3.0% for females versus 3.9% for males, χ^2 test $P>0.05$. According to the logistic regression model results, no association between gender and AEs occurrence seems to exist. A statistically significant gender difference in the percentage of drug-related AEs emerged (37.6% in females vs 20.8% in males, χ^2 $P=0.0039$). Slightly significantly more AEs in females were addressed with treatment compared with males (78.1% vs 66.7%, χ^2 $P=0.0485$). Total serious AEs (SAEs) were 47 (72% in males). The frequency of patients with ≥1 SAE was 0.6% in females versus 1.2% in males (χ^2 test $P=0.0246$).

Conclusion: This safety analysis on a large sample of almost 5,000 patients 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 from a gender-specific perspective.

Keywords: gender, drugs, safety, adverse events, meta-analysis

Introduction

Clinical data suggest that male and female patients exhibit differences regarding the pharmacology and toxicity of medications[1] and differ in their response to drug treatment, not only as a result of physiological differences, such as body weight, surface area, and extracellular and intracellular water, but also in terms of differences in pharmacokinetics (PK) and pharmacodynamics (PD).[2–4] It is known that sex hormones influence drug absorption, distribution, metabolism, PD, and adverse events (AEs).[5] In 2001, on the basis of its Adverse Events Reporting System, the US Food and Drug

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Administration stated that females experience more and more serious AEs (SAEs) than males.[6] It has been hypothesized that this may be due to overdosing, different PK and PD, the fact that females are more likely to report AEs than males, or that females take more medications than males. It has been shown that females use more medicines than males do and have a higher rate of chronic diseases, but they also generally pay more attention to their health and have more consciousness and care about themselves.[6]

Despite the increasing evidence of physiological and pathological differences between genders, beyond those related to reproduction,[7–11] females still represent a small percentage (22%) of participants in Phase I trials which are essential to verify drug dosage, AEs, and safety.[12] Medical research has been conducted for decades with a large prevalence of male participants in clinical studies, yet the findings of these studies have often been applied to both genders.[12] Only with the new millennium has this changed with the European Union promoting females's participation in research projects and the World Health Organization including gender medicine in the Equity Act in order to achieve gender-appropriate care.[13] However, to date, the analyses provided by the pharmaceutical industry to the regulatory authorities often do not classify safety and efficacy data by gender.

In 2013, the Italian Drug Agency (Agenzia Italiana del Farmaco) invited pharmaceutical companies to process data divided by gender during the submission of regulatory documentation, so as to highlight possible differences.[14] In the same year, Novartis Italy put in place a wide gender-medicine project, called MetaGeM, which included analysis by gender of the data from nine previously conducted observational studies. These studies were performed between 2002 and 2013, and covered a range of different clinical areas, including immune-mediated disorders (psoriasis and psoriatic arthritis), transplantation medicine (liver and kidney transplants), infectious diseases (hepatitis B), and the central nervous system (Parkinson's disease and Alzheimer's disease [AD]). The aim of the MetaGeM project was to analyze and describe clinical outcomes, therapeutic approaches, and safety data by gender, using post hoc analyses and meta-analyses, in order to explore possible gender differences. The methodology of the MetaGeM project has been described in detail elsewhere.[15] The present paper reports the results of the overall safety analysis of the MetaGeM studies, aimed at evaluating possible gender differences in the incidence and severity of AEs and the potential association between gender and safety.

Methods

Seven of the nine observational studies of the MetaGeM project were included in this safety analysis on 2,612 (53.6%) males and 2,258 (46.4%) females: they are listed and briefly described in Table 1. With regard to the two excluded studies, the GENDER-ATTENTION ("The female in her real dimension: effect of gender and hormonal status on adverse events' incidence in psoriatic patients treated with cyclosporine") study (Colombo et al, unpublished data, 2013a; Colombo et al, unpublished data, 2013b; Colombo et al, unpublished data, 2014a; Colombo et al, unpublished data, 2014b; Colombo et al, unpublished data, 2016) was not included because a gender-specific safety assessment was the primary objective of the study itself, while the Studio Osservazionale Italiano per la valutazione dell'insUfficienza Renale in pazienti con trapianto di Fegato (SURF) ("Italian Observational Study for the evaluation of renal insufficiency in liver transplant patients") study (Donato et al, unpublished data, 2013) was also not considered because it did not include safety data collection.

An AE was defined as any unfavorable or unintended sign, symptom, or disease that occurred from the time the signed informed consent was obtained until the end of the patient observation period. An AE was defined as a SAE if it resulted in death, was judged life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or caused a congenital anomaly/birth defect in the child of the observed patient. In cases where such information was available, the possible relationship with therapy, as evaluated by the investigator, was reported.

Data were collected between February 2002 (first patient first visit; PSYCHAE study[16,17]) and July 2013 (last patient last visit; ICEBERG study [Rizzetto et al, unpublished data, 2011; Bandiera et al, unpublished data, 2012]); first patient first visit and last patient last visit for each study are shown in Table 1. Monitoring visits were conducted to verify whether enrollment was performed consecutively and according to inclusion/exclusion criteria. Moreover, before statistical analysis, a data cleaning process was run to check the collected data for completeness and accuracy.

Patients were considered evaluable for this analysis if they were evaluable for the individual study in which they participated and if gender was recorded in the case report form (CRF), as detailed elsewhere.[16–23]

Evaluable patients were described according to sociodemographic (such as age) and clinical (such as ongoing specific therapies) features. Moreover, male and female patients

Table 1 MetaGeM observational studies and patients included in the analysis

Area (disease)	Study	Patient population and study objectives	Ongoing specific therapies	FPFV	LPLV	Females		Males		Total
						N	%	N	%	N
CNS	DEEP[18,19] (Early detection of wearing off in Parkinson's disease)	Assessment of wearing off in patients with Parkinson's disease under treatment with levodopa and/or dopamine agonists without dementia	Levodopa and/or dopamine agonists	March 2010	November 2010	236	38.3	381	61.8	617
CNS	EVOLUTION[20] (Behavioral symptoms in AD: evaluation of patients treated with ChEI)	Evaluation of changes in cognitive and affective domain severity in mild-to-moderate AD patients undergoing a switch of ChEI for lack or loss of efficacy and/or tolerability/compliance	Switch from one ChEI to another after ≥6 months, due to lack or loss of efficacy (reduction of ≥2 points of MMSE score in the last 6 months) and/or reduced compliance (due to side effects or nonadherence to recommended dosing)	April 2010	September 2011	379	59.7	256	40.3	635
CNS	AXEPT[21] (AD: examination of patient compliance and caregiver satisfaction)	Comparing compliance to treatment of community-dwelling patients with mild-to-moderate AD treated with transdermal or oral drugs and caregiver satisfaction in a real clinical setting	ChEIs (oral or transdermal) or memantine in monotherapy	September 2010	January 2011	544	63.6	311	36.4	855
Infectious diseases	ICEBERG (Natural history of chronic hepatitis B virus infection: an observational study on asymptomatic HBsAg carriers)[a]	Evaluation of natural history of disease in asymptomatic, untreated HBsAg carriers	NA	December 2008	July 2013	377	42.1	518	57.9	895
Dermatology (psoriasis)	PSYCHAE[16,22] (Psoriasis: survey for the control of anxiety and depression)	Assessing the prevalence and evolution of psychological distress in a large series of Italian patients with psoriasis followed at dermatological centers	Phototherapy, systemic medications, non-pharmacological therapy, topical treatments	February 2002	May 2004	309	39.3	477	60.7	786
Dermatology (psoriasis)	SYNERGY[17] (Observational study of infectious events in psoriasis complicated by active psoriatic arthritis)	Evaluation of infectious events in patients with psoriasis and psoriatic arthritis receiving systemic immunosuppressive therapy, including CsA	CsA ± other immune-suppressants	March 2010	January 2012	104	46.2	121	53.8	225

(*Continued*)

Table 1 (*Continued*)

Area (disease)	Study	Patient population and study objectives	Ongoing specific therapies	FPFV	LPLV	Females		Males		Total
						N	%	N	%	N
Dermatology (psoriasis)	GENDER-ATTENTION[b,*] (The female in her real dimension: effect of gender and hormonal status on adverse events' incidence in psoriatic patients treated with CsA)	Evaluation of the differences in side effects' incidence rate (as patient leaflet) between females (stratified by fertile/menopausal status) and age-matched males in patients with plaque psoriasis treated with CsA								
Transplants	CETRA[23] (Complications related to gastro-enteric symptoms in renal transplant patients) (Ponticelli)	Evaluation of the prevalence of gastrointestinal symptoms in patients with functioning, stable renal transplant and no underlying diseases that could cause gastrointestinal symptoms	CsA + azathioprine + CS CsA + MMF CsA + MMF + CS CsA + CS Tacrolimus + MMF + CS Tacrolimus + CS	June 2006	April 2008	309	36.1	548	63.9	857
Transplants	SURF* (Italian Observational Study for the evaluation of Renal Insufficiency in liver transplant patients) (Donato et al, unpublished data, 2013)	Evaluation of the proportion of patients with eGFR <60 mL/min/1.73 m^2 at inclusion visit and 12 months after the inclusion visit								
	Total evaluable patients					**2,258**	**46.4**	**2,612**	**53.6**	**4,870**

Notes: *Study not considered in the present analysis. [a]Rizzetto et al, unpublished data, 2011; Bandiera et al, unpublished data, 2012. [b]Colombo et al, unpublished data, 2013a; Colombo et al, unpublished data, 2013b; Colombo et al, unpublished data, 2014a; Colombo et al, unpublished data, 2014b; Colombo et al, unpublished data, 2016.

Abbreviations: AD, Alzheimer's disease; ChEI, cholinesterase inhibitors; CNS, central nervous system; CsA, cyclosporine; CS, corticosteroids; eGFR, epidermal growth factor receptor; FPFV, first patient first visit; LPLV, last patient last visit; MMF, mycophenolate mofetil; HBsAg, Hepatitis B surface antigen; MMSE, Mini Mental State Examination; NA, not available.

were compared with regard to the main safety variables: AE occurrence and characteristics (description, intensity, possible correlation with a drug, evolution, and therapeutic intervention, if any), and SAE occurrence and description. Comparisons were performed by Student's *t*-test, χ^2 test, or Fisher's exact test as appropriate. For the post hoc analyses, all *P*-values presented are exploratory. Patients with missing data in selected parameters were not excluded from analysis, but were simply not evaluated for these parameters.

Data collection was performed for all studies through the CRF; however, not all variables of interest were present in all studies or, if present, not all had the same answer categories. For these reasons, AE CRF fields that were common to all studies were identified through a preliminary analysis, and a new variable for each outcome of interest (eg, AE description, AE intensity) was created considering the value in each study. Fields that were missing in some studies were analyzed only where present.

Different answer modalities were present in the original CRFs for AE intensity, possible correlation of AE with a drug, and AE evolution, and so recoding was performed. Briefly, the AE intensity was classified as mild, moderate, high, or not determined, as originally reported in most studies. In the EVOLUTION study, grade 1 intensity (based on Common Terminology Criteria for Adverse Events v3.0) was considered as mild, grade 2 as moderate, and grades 3–5 as high, while in the ICEBERG study (Rizzetto et al, unpublished data, 2011; Bandiera et al, unpublished data, 2012), AEs defined as severe were considered to be of high intensity. For the CETRA study, the intensity of AEs could not be analyzed because this variable was not collected on the CRF. Possible correlation with a drug was defined as present (yes), absent (no), or not determined; if changes in therapy had been introduced, these were evaluated in terms of dosage escalation or reduction, therapy discontinuation, or "other". Concerning their evolution, AEs were considered as resolved (including resolved without sequelae), unresolved, toward resolution, resolved without sequelae, or resolution unknown. SAEs were reported as death, hospitalization, disability, persistent or significant inability, life-threatening events, or not determined.

As supportive analysis, a logistic regression model was estimated to evaluate the association between gender (male, female) and outcome ("the patient had at least one AE during the study"). The model provided estimates of the odds ratios of experiencing an AE in female versus male patients. All analyses were performed with SAS v9.2 and Enterprise Guide v4.3. (SAS v9.2: Copyright © 2009 by SAS Institute Inc., Cary, NC, USA; Enterprise Guide v4.3 Copyright © 2006–2010 by SAS Institute Inc., Cary, NC, USA).

Results

In total, 4,870 patients, 46% females and 54% males, were included in the analysis, as detailed in Table 1. Age by gender and study is reported in Table 2: overall, mean age was higher in females (61.2±18.3 years) than in males (56.3±16.6 years). Disease-specific therapies ongoing at enrollment in the studies are summarized in Table 3.

Overall, 264 AEs were reported, 59.1% in males; Table 4 summarizes the type of AEs, according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class.

There was no significant gender difference in the percentage of patients with at least one AE (ie, patients with 1, 2, or ≥3 AEs): 3.0% for females versus 3.9% for males, χ^2 test $P \geq 0.05$. Details about the occurrence and intensity of AEs by gender and study are reported in Table 5. The results of the logistic regression model also showed no association

Table 2 Demographic characteristics of patients

Study	Mean age (years)	Standard deviation	≥50 years N (%)
PSYCHAE[16,22]			
Females	43.7	13.0	123 (39.8)
Males	45.3	12.1	184 (38.6)
Total	44.7	12.5	307 (39.1)
DEEP[18,19]			
Females	67.0	8.9	228 (96.6)
Males	66.6	9.4	362 (95.0)
Total	66.8	9.2	590 (95.6)
EVOLUTION[20,a]			
Females	77.2	7.1	378 (99.7)
Males	76.0	6.9	256 (100.0)
Total	76.7	7.0	634 (99.8)
AXEPT[21,b]			
Females	78.2	6.4	544 (100.0)
Males	76.9	6.6	311 (100.0)
Total	77.7	6.5	855 (100.0)
ICEBERG[d]			
Females	44.9	12.9	158 (41.9)
Males	45.4	11.6	208 (40.2)
Total	45.2	12.2	366 (40.9)
SYNERGY[17]			
Females	50.8	12.5	54 (51.9)
Males	48.9	12.8	57 (47.1)
Total	49.8	12.7	111 (49.3)
CETRA[23]			
Females	48.1	11.6	146 (47.2)
Males	49.6	12.2	287 (52.4)
Total	49.1	12.0	433 (50.5)
Total evaluable patients[c]			
Females	61.2	18.3	1,631 (72.2)
Males	56.3	16.6	1,665 (63.7)
Total	58.6	17.6	3,296 (67.7)

Notes: Student's *t*-test *P*-values (males versus females): [a]0.0427; [b]0.0045; [c]0.0001. [d]Rizzetto et al, unpublished data, 2011; Bandiera et al, unpublished data, 2012. Percentages calculated for the total number of evaluable patients.

Table 3 Specific medications taken at inclusion in the study

Study	Medications	Females N (%)	Males N (%)	Total evaluable patients, N (%)
DEEP[18,19]	DA	11 (4.7)	15 (3.9)	26 (4.2)
	DA + MAO-B inhibitors	17 (7.2)	36 (9.4)	53 (8.6)
	Levodopa	29 (12.3)	35 (9.2)	64 (10.4)
	Levodopa + DA	59 (25.0)	77 (20.2)	136 (22.0)
	Levodopa + DA + COMT inhibitors	41 (17.4)	73 (19.2)	114 (18.5)
	Levodopa + DA + MAO-B inhibitors	28 (11.9)	56 (14.7)	84 (13.6)
	Levodopa + DA + MAO-B inhibitors + COMT inhibitors	24 (10.2)	28 (7.3)	52 (8.4)
	Levodopa + COMT inhibitors	12 (5.1)	24 (6.3)	36 (5.8)
	Levodopa + MAO-B inhibitors	13 (5.5)	30 (7.9)	43 (7.0)
	Levodopa + MAO-B inhibitors + COMT inhibitors	2 (0.8)	7 (1.8)	9 (1.5)
	Total evaluable patients	236 (100.0)	381 (100.0)	617 (100.0)
EVOLUTION[20]	Donepezil (oral)	264 (69.7)	178 (69.5)	442 (69.6)
	Galantamine (oral)	33 (8.7)	18 (7.0)	51 (8.0)
	Rivastigmine (patch)	52 (13.7)	24 (9.4)	76 (12.0)
	Rivastigmine (oral)	30 (7.9)	36 (14.1)	66 (10.4)
	Total evaluable patients	379 (100.0)	256 (100.0)	635 (100.0)
AXEPT[21]	Donepezil (oral)	142 (26.1)	78 (25.1)	220 (25.7)
	Galantamine (oral)	21 (3.9)	12 (3.9)	33 (3.9)
	Memantine (oral)	107 (19.7)	70 (22.5)	177 (20.7)
	Rivastigmine (patch)	253 (46.5)	141 (45.3)	394 (46.1)
	Rivastigmine (oral)	21 (3.9)	10 (3.2)	31 (3.6)
	Total evaluable patients	544 (100.0)	311 (100.0)	855 (100.0)
CETRA[23]	CsA + AZA + steroids	25 (8.1)	29 (5.3)	54 (6.3)
	CsA + MMF	21 (6.8)	33 (6.0)	54 (6.3)
	CsA + MMF + steroids	42 (13.6)	95 (17.3)	137 (16.0)
	CsA + steroids	31 (10.0)	49 (8.9)	80 (9.3)
	Tacrolimus + MMF + steroids	46 (14.9)	75 (13.7)	121 (14.1)
	Tacrolimus + steroids	20 (6.5)	33 (6.0)	53 (6.2)
	Total evaluable patients	309 (100.0)	548 (100.0)	857 (100.0)
PSYCHAE[16,22]	Phototherapy	88 (28.5)	178 (37.3)	266 (33.8)
	Systemic drug therapy	111 (35.9)	192 (40.3)	303 (38.5)
	Non-pharmacologic therapy	83 (26.9)	131 (27.5)	214 (27.2)
	Topical therapy	224 (72.5)	357 (74.8)	581 (73.9)
	Total evaluable patients	309 (100.0)	477 (100.0)	786 (100.0)
SYNERGY[17]	Local infiltrations ≤12 months before baseline	1 (1.0)	4 (3.3)	5 (2.2)
	Systemic therapy for psoriasis and PsA ≤12 months before baseline	104 (100.0)	120 (99.2)	224 (99.6)
	Topical therapy for psoriasis and PsA ≤12 months before baseline	79 (76.0)	96 (79.3)	175 (77.8)
	Total evaluable patients	104 (100.0)	121 (100.0)	225 (100.0)

Abbreviations: AZA, azathioprine; CsA, cyclosporine; COMT, catechol O-methyltransferase; DA, dopamine; MAO, monoamino-oxidase; MMF, mycophenolate mofetil; PsA, psoriatic arthritis; MAO-B, monoamine oxidase-B.

between gender and AE occurrence: odds ratio =0.764 (females vs males), 95% confidence interval: 0.559–1.044, but a statistically significant gender difference in the percentage of drug-related AEs emerged (37.6% in females vs 20.8% in males, χ^2 test P=0.0039). AE evolution is depicted in Figure 1. Overall, more AEs were addressed with some kind of treatment in females compared with males (78.1% vs 66.7%, χ^2 P=0.0485).

Total SAEs were 47 (72% in males). The frequency of patients with ≥1 SAE was 0.6% in females versus 1.2% in males (χ^2 test P=0.0246). Number and type of SAEs are detailed in Table 6.

Discussion

Gender-specific medicine is the study of how diseases differ between males and females in terms of prevention,

Table 4 AEs according to system organ class (MedDRA)

System organ class MedDRA	Total	%
Infections and infestations	48	18.2
Gastrointestinal disorders	27	10.2
General disorders and administration site conditions	21	8.0
Musculoskeletal and connective tissue disorders	17	6.4
Renal and urinary disorders	17	6.4
Skin and subcutaneous tissue disorders	14	5.3
Metabolism and nutrition disorders	12	4.5
Nervous system disorders	11	4.2
Respiratory, thoracic and mediastinal disorders	10	3.8
Investigations	10	3.8
Injury, poisoning, and procedural complications	8	3.0
Hepatobiliary disorders	7	2.7
Immune system disorders	7	2.7
Blood and lymphatic system disorders	7	2.7
Psychiatric disorders	7	2.7
Neoplasms benign, malignant, and unspecified	6	2.3
Reproductive system and breast disorders	5	1.9
Cardiac disorders	5	1.9
Vascular disorders	5	1.9
Eye disorders	3	1.1
Surgical and medical procedures	3	1.1
SOC not attributed	14	5.3
Total number of occurred AEs	264	100

Abbreviations: AEs, adverse events; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class.

clinical manifestations, therapeutic approach, outcomes and tolerability, prognosis, and psychological and social impact. There has been increasing evidence in recent years of physiological and pathological differences between the genders. Focusing on the diseases examined in the studies included in our analysis, many gender differences have been reported for patients with psoriasis and psoriatic arthritis, in terms of epidemiology,[24] pattern and burden of disease,[25] search for care,[26] and choice of therapy;[27,28] for example, peripheral joint involvement, pain, and functional impairment are more frequent for female than for male patients with psoriasis.[29–32] Moreover, the PSYCHAE study[16] pointed out that the psychological status of females was also worse than that of males, independently of the severity of psoriasis. There is also an extensive literature on gender differences in AD, as recently reviewed by Li and Singh.[33] Clinical studies have shown differences between males and females in specific cognitive ability domains and risk of AD at later age. Several major biological hypotheses have been postulated, such as differences in age-related sex hormone reduction (estrogens, progesterone, testosterone), impact from risks of other diseases (diabetes, depression), and age-related decline in brain volume. In Parkinson's disease as well, gender-related differences have been recognized, although these are still poorly understood. Prevalence and incidence of Parkinson's disease are significantly higher in males than in females.[34,35] From a clinical point of view, females with Parkinson's disease have shown worse capacity in activities of daily living and more severity of levodopa-induced dyskinesia in several studies,[36–38] while male gender was shown to predict worse rigidity score and higher risk for sleep behavior disorder, dementia, and death.[37,39–41] A 2014 cross-sectional survey[42] found that males reported a greater disease burden and greater daily levodopa equivalent doses than females. The greater burden of disease score in males was significantly associated with gender even after controlling for age and disease duration. Concerning transplants, gender-based disparities have been observed in post-liver transplantation outcomes, together with a continuous decline in the number of liver transplantations in females.[43]

The effect of gender on drug tolerability has begun to raise interest only in recent years, mainly resulting in the observation that females experience more frequent and more SAEs than males, possibly due to different PK and PD, higher rates of AE reporting, or greater use of medications in females compared to males.[6,44–46] Clinical research sponsored by Novartis Italy in the past decade included several large observational studies in important medical areas, including psoriasis.[16,17,22,47] Central nervous system disorders, such as Parkinson's disease and AD,[18–21] and transplantation,[23] but none of those studies, except one (the aforementioned GENDER-ATTENTION study [Colombo et al, unpublished data, 2013a; Colombo et al, unpublished data, 2013b; Colombo et al, unpublished data, 2014a; Colombo et al, unpublished data, 2014b; Colombo et al, unpublished data, 2016]), adopted a gender-specific approach in data analysis. Based on the increasing interest in gender medicine and prompted by the large quantity of clinical data available through these large national studies, it was decided to reanalyze these data from a gender perspective (the MetaGeM project). This paper focuses on the overall safety data from seven MetaGeM studies.

The overall MetaGeM sample (N=4,870) consisted of 2,612 (53.6%) males, with females being predominant only in the two AD studies, EVOLUTION and AXEPT (59.7% and 63.6%, respectively, of those enrolled are female). This prevalence of female patients in the AD studies probably accounts for the overall higher mean age in females compared with males.

There were no significant gender differences in the frequency of patients with at least one AE (3.0% for females vs 3.9% for males, χ^2 test $P>0.05$), with 59.1% of global AEs occurring in males. Considering only those reported as drug-related AEs, the incidence was significantly higher in females, and this is consistent with several reports revealing

Table 5 Occurrence of AEs during the study

Study	Patients with 1 AE N (%)	Patients with 2 AEs N (%)	Patients with ≥3 AEs N (%)	Total AEs N	Mild intensity AEs, N	Moderate intensity AEs, N	High intensity AEs, N
PSYCHAE[16,22]							
Females	2 (0.6)	0 (0)	0 (0)	2	0	1	0
Males	3 (0.6)	1 (0.2)	0 (0)	5	2	1	1
Total	5 (0.6)	1 (0.1)	0 (0)	7			
DEEP[18,19]							
Females	1 (0.4)	1 (0.4)	0 (0)	3	1	2	0
Males	3 (0.4)	0 (0)	0 (0)	3	2	1	0
Total	4 (0.6)	1 (0.2)	0 (0)	6			
EVOLUTION[20]							
Females	12 (3.2)	0 (0)	3 (0.8)	24	12	6	6
Males	10 (3.9)	1 (0.4)	0 (0)	12	5	3	2
Total	22 (3.5)	1 (0.2)	3 (0.5)	36			
AXEPT[21]							
Females	1 (0.2)	0 (0)	0 (0)	1	0	0	0
Males	0 (0)	1 (0.3)	0 (0)	2	2	0	0
Total	1 (0.1)	1 (0.1)	0 (0)	3			
ICEBERG[a]							
Females	3 (0.8)	0 (0)	0 (0)	3	2	0	1
Males	6 (1.2)	1 (0.2)	0 (0)	8	2	1	5
Total	9 (1.0)	1 (0.1)	0 (0)	11			
SYNERGY[17]							
Females	7 (6.7)	0 (0)	0 (0)	7	2	4	0
Males	5 (4.1)	3 (2.5)	0 (0)	11	5	6	0
Total	12 (5.3)	3 (1.3)	0 (0)	18			
CETRA[23]							
Females	17 (5.5)	15 (4.9)	6 (1.9)	68	ND	ND	ND
Males	44 (8.0)	8 (1.5)	16 (2.9)	115	ND	ND	ND
Total	61 (7.1)	23 (2.7)	22 (2.6)	183			
Total evaluable patients							
Females	43 (1.9)	16 (0.7)	9 (0.4)	108			
Males	71 (2.7)	15 (0.6)	16 (0.6)	156			
Total	114 (2.3)	31 (0.6)	25 (0.5)	264			

Notes: Percentages calculated over total number of evaluable patients. [a]Rizzetto et al, unpublished data, 2011; Bandiera et al, unpublished data, 2012.
Abbreviations: AE, adverse event; ND, not determined.

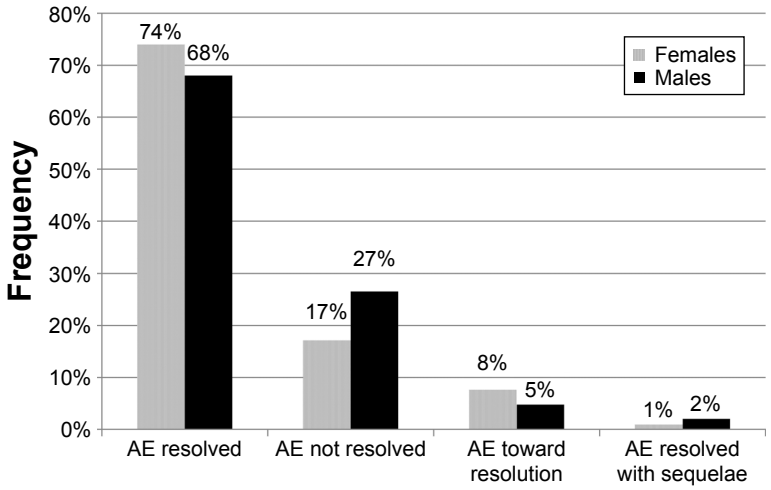

Figure 1 Evolution of AEs by gender.
Note: Percentages calculated over total number of AEs during observation with available data on evolution (N=256).
Abbreviation: AEs, adverse events.

Table 6 Serious adverse events (SAEs) occurred during study

Study	Patients with ≥1 SAE during in the study	Females N (%)	Males N (%)	Total evaluable patients, N (%)
DEEP[18,19]	No SAE	236 (100.0)	381 (100.0)	617 (100.0)
	Total evaluable patients	236 (100.0)	381 (100.0)	617 (100.0)
EVOLUTION[20]	No SAE	378 (99.7)	253 (98.8)	631 (99.4)
	≥1 SAE	1 (0.3)	3 (1.2)	4 (0.6)
	Total evaluable patients	379 (100.0)	256 (100.0)	635 (100.0)
AXEPT[21]	No SAE	544 (100.0)	311 (100.0)	855 (100.0)
	Total evaluable patients	544 (100.0)	311 (100.0)	855 (100.0)
CETRA[23]	No SAE	299 (96.8)	526 (96.0)	825 (96.3)
	≥1 SAE	10 (3.2)	22 (4.0)	32 (3.7)
	Total evaluable patients	309 (100.0)	548 (100.0)	857 (100.0)
PSYCHAE[16,22]	No SAE	309 (100.0)	477 (100.0)	786 (100.0)
	Total evaluable patients	309 (100.0)	477 (100.0)	786 (100.0)
SYNERGY[17]	No SAE	104 (100.0)	120 (99.2)	224 (99.6)
	≥1 SAE	0 (0)	1 (0.8)	1 (0.4)
	Total evaluable patients	104 (100.0)	121 (100.0)	225 (100.0)
ICEBERG[d]	No SAE	375 (99.5)	513 (99.0)	888 (99.2)
	≥1 SAE	2 (0.5)	5 (1.0)	7 (0.8)
	Total evaluable patients	377 (100.0)	518 (100.0)	895 (100.0)
	Total pts with ≥1 SAE[a]	13 (0.6)	31 (1.2)[b]	44
	Total SAE	13 (28)	34 (72)[c]	47
	Deaths	0	2	2
	Persistent or significant disability or inability	0	2	2
	Hospitalizations	13	27	40
	Life-threatening events	0	3	3
	Total evaluable patients	2,258 (100.0)	2,612 (100.0)	4,870 (100.0)

Notes: [a]χ^2 test, P=0.0246. [b]Percentages calculated for the total number of evaluable patients. [c]Percentages calculated for the total number of SAEs. [d]Rizzetto et al, unpublished data, 2011; Bandiera et al, unpublished data, 2012.
Abbreviation: pts, patients.

that females are more prone to adverse drug reactions (ADRs) than males, as confirmed by the evidence that eight of ten drugs that have been dropped out from the US market were responsible for more ADRs in females than in males. Indeed, risk factors for ADRs, such as polytherapy, aging (females become generally older than males), and depression, are in general more frequent in females than in males.[44–46,48,49] Other factors hypothesized to explain why females usually report more ADRs are the fact that females have a higher prevalence of pain (headache, migraine, musculoskeletal pain) and pay greater attention to their health status. Moreover, physiological aspects, such as menstrual cycles, pregnancy, and menopause, are likely to have a relevant impact on the PK and PD of drugs.

Unexpectedly, we found that 2% of SAEs occurred in males, and the frequency of patients reporting at least one SAE was significantly higher in males, despite the older mean age of females compared with males. These results are in contrast with the large quantity of published data showing that females experience more AEs and that these are generally also more serious.[6,30–32] However, it has to be considered that the overall patient population was fairly unbalanced by the CETRA study on renal transplantation (inclusion criteria: age ≥18 years, renal allograft functioning for at least 6 months, and serum creatinine level <2.5 mg/dL), which included 64% male patients and accounted for 77% of total SAEs (36 of 47). This may be reasonably explained by the fact that the CETRA patients were transplanted patients, frequently hospitalized for transplant-related events. For these reasons, in order to have a more homogeneous population, we repeated the analysis excluding CETRA patients. This analysis showed no significant difference between the genders in terms of SAEs (0.2% of females vs 0.4% of males had at least one SAE; χ^2 test, $P>0.05$).

We had no adequate information about the degree of disease severity in the patients considered for this analysis and therefore were unable to analyze for possible correlations between severity of disease and incidence of AE; however, we hypothesized that the type and number of therapies administered could mirror the severity of the disease, at least for the DEEP study (Parkinson's disease) and the PSYCHAE and SYNERGY studies (psoriasis ± psoriatic arthritis). Following specific analyses, we found no correlations between the incidence of AEs and the number of drugs administered

to patients (1–2 and ≥3) in the DEEP study, or the type of therapy (topical or systemic) in the other two studies in psoriasis. This seems to confirm that the observed gender differences were not biased by the severity of the disease.

Limitations

Our study has some limitations. As a post hoc analysis, it was not originally designed to assess gender differences in patients' safety profile, and statistical analysis was mainly descriptive with only explorative *P*-values. Moreover, owing to the inclusion of several studies, large differences in patient population, study design, and ongoing treatments have to be taken into account. For this reason, a common approach for data cleaning, recoding, and statistical analysis was followed. Finally, one single study, CETRA, which studied the quite complex and serious clinical condition of renal transplantation, accounted for the majority of AEs (183/264) and SAEs (36/47), and this may have strongly affected the results of our analysis.

Conclusion

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, within the considered disease areas, of possible gender differences in drug tolerability, which may be helpful in more accurately designing future clinical trials from a gender-specific perspective.

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Disclosure

DC is a part-time employee of Novartis Farma Italy and received grants from Allergan and Aventis. EZ and MN are employees of Novartis Farma Italy. SR and AO are employees of MediNeos srl. GB was an employee of Novartis Farma Italy during study execution and manuscript submission, but now is an employee of UCB Pharma Italy. The authors report no other conflicts of interest in this work.

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