Rosiglitazone and Risk of Cancer

A meta-analysis of randomized clinical trials

MATTEO MONAMI, MD, PHD
CATERINA LAMANNA, MD
NICCOLÒ MARCHIONNI, MD
EDOARDO MANNUCCI, MD

OBJECTIVE — Despite experimental data suggesting a protective effect of peroxisome proliferator–activated receptor-γ agonists with respect to malignancies, results of available epidemiological studies on the incidence of cancer in rosiglitazone-treated patients are not univocal. The aim of this meta-analysis of randomized clinical trials is to assess the effect of rosiglitazone on the incidence of cancer.

RESEARCH DESIGN AND METHODS — Randomized clinical trials of rosiglitazone with duration of >24 weeks were retrieved through Medline and from the GlaxoSmithKline Web site, which reports main results of all trials sponsored by GlaxoSmithKline; incident malignancies were retrieved from the summary of serious adverse events. Proportions of outcome measures across treatment groups were compared by odds ratios (ORs) and 95% CI. Considering differences in the duration of follow-up among treatment arms in some of the trials, we also calculated the incidence of cancer in rosiglitazone and control groups.

RESULTS — Eighty trials, enrolling 16,332 and 12,522 patients in the rosiglitazone and comparator groups, respectively, were retrieved. Rosiglitazone was not associated with a significant modification of the risk of cancer (OR 0.91 [95% CI 0.71–1.16], $P = 0.44$). The incidence of malignancies was significantly lower in rosiglitazone-treated patients than in control groups (0.23 [0.19–0.26] vs. 0.44 [0.34–0.58] cases/100 patient-years; $P < 0.05$).

CONCLUSIONS — The use of rosiglitazone appears to be safe in terms of incidence of cancer, whereas its possible protective effect needs to be further investigated.

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Two epidemiological surveys provided discordant results on the effects of rosiglitazone on the incidence of malignancies. One study reported a specific reduction in the incidence of lung cancer (1), whereas another survey suggested an increased risk of malignancies, without providing information on types of cancer (2).

A hypothetical anticancer effect of thiazolidinediones has been suggested on the basis of their pharmacological profile of action. The antimitotic and prodifferentiating effects of peroxisome proliferator–activated receptor (PPAR)-γ agonists, which have been described in vitro and in animal models (3–5), suggested the possible use of these drugs as anticancer therapy, although the results of preliminary trials were contradictory (6–10). On the other hand, the mechanisms underlying a possible mitogenic effect of PPAR-γ activators have not been identified so far. The aim of the present meta-analysis is to assess the risk of cancer associated with rosiglitazone treatment, compared either with placebo or active hypoglycemic drugs.

RESEARCH DESIGN AND METHODS

— Trials were identified through a search of a Web site of GlaxoSmithKline (GSK) (11), manufacturer of rosiglitazone, which contains results of all completed trials sponsored by GSK, with a description of all serious adverse events (including those considered not related to study drug), such as incident malignancies. Published trials sponsored by other companies or by academic institutions were retrieved through a Medline search for all randomized controlled trials with rosiglitazone performed in humans with results published in English up to 5 February 2008. For each trial, all fatal and nonfatal serious adverse events in each treatment arm are listed with a brief description. All studies comparing rosiglitazone with placebo or other active drugs, with a duration >24 weeks, were included in the analysis. Studies of shorter duration were excluded, considering that a brief exposure to a drug is unlikely to have any impact on the incidence of cancer. Occurrences of fatal or nonfatal cancer were extracted from serious adverse events.

After the exclusion of trials with zero events, odds ratios (ORs) and 95% CI, with the Mantel-Haenszel (MH)-OR weighting procedure, were calculated using a random effect model. This procedure was chosen to overcome the limitations of the Peto method (12–14), which had been used in a previous meta-analysis on cardiovascular effects of rosiglitazone (15). In fact, the Peto method overestimates differences between treatments when a large number of small trials, with few events, are included in a meta-analysis (12–14). Separate analyses were performed, whenever possible, for trials with different comparators and for those performed in type 2 diabetic or nondiabetic patients, as well as for trials with duration ≥52 weeks. Separate analyses were also performed for the most common individual types of cancer.

Considering that in the largest trial included in the analysis (16) the duration of follow-up in the rosiglitazone arm is longer than in comparators (17), we also calculated the actual incidence density of cancer in different treatment groups using a random effect model, assuming that rates of loss at follow-up, mortality, and incidence of malignancies were constant throughout the duration of each trial; this analysis also included trials with zero events. Furthermore, after determination of effect sizes for individual trials, ratios

From the Department of Cardiovascular Medicine, Section of Geriatric Cardiology, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy.
Corresponding author: Edoardo Mannucci, edoardo.mannucci@unifi.it.
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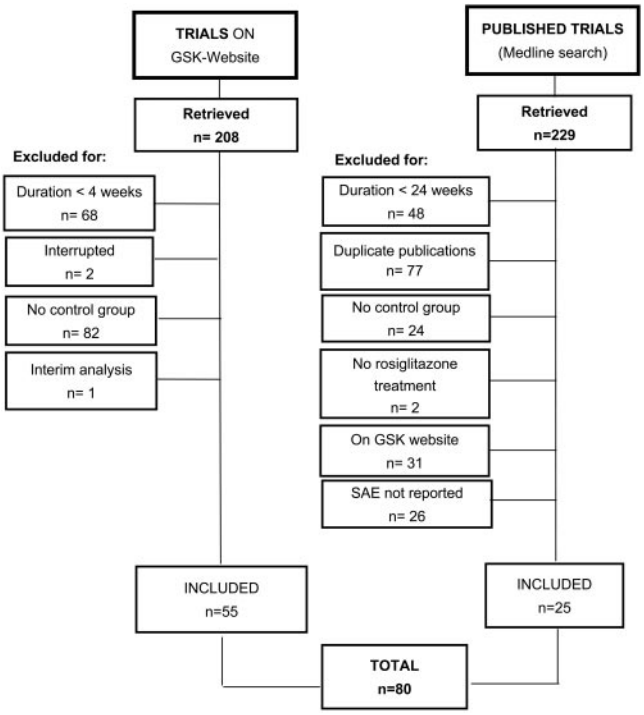

Figure 1—*Flow diagram of the trials evaluated for inclusion in the meta-analysis. SAE, serious adverse events.*

between incidence densities were calculated for each trial and combined to obtain a pooled rate ratio. All of the analyses were performed using Comprehensive Meta Analysis (version 2.2.046; Englewood, NJ).

RESULTS — The trial flow is summarized in Fig. 1. The 80 trials included in the analysis enrolled 16,332 and 12,522 patients for rosiglitazone and comparators (15,700 and 18,050 patient-years), respectively, with a weighted mean age of 55.3 years. Of the retrieved trials, 63 and 17 were performed on type 2 diabetic patients (mean A1C 8.1%) or on subjects with different conditions, respectively (Table 1). Most (25 of 51) of the published trials not present on the GSK Web site (11) did not report a detailed description of serious adverse events, including malignancies; only two malignancies had been observed in those trials for which this information was available. A complete list of published trials not on GSK Web site, either included or not included in the meta-analysis, is reported in the online appendix (available at http://dx.doi.org/10.2337/dc07-2308).

The number of incident malignancies reported in each trial is summarized in Table 1. Of the 302 cases of cancer, 42 (13.9%) were gastrointestinal, 13 (4.3%) pancreatic, 26 (8.6%) pulmonary, 35 (11.6%) of mammary gland/female genital tract, 36 (11.9%) of male urogenital tract, and 105 (34.8%) of other known origin; the type of cancer was not specified in 45 (14.9%) cases. No difference was observed in the proportion of cases between patients allocated to rosiglitazone and comparators. The overall MH-OR [95% CI] for rosiglitazone compared with control groups was 0.91 ([0.71–1.16]; $P = 0.44$). More than one-half of all malignancies were observed in one large trial, A Diabetes Outcome Progression Trial (ADOPT); the MH-OR after the exclusion of this study was 0.92 (0.61–1.39). When trials with a duration ≥52 weeks were analyzed separately, the MH-OR for rosiglitazone was 0.86 (0.66–1.14). Similar results were obtained for nondiabetic and type 2 diabetic patients (0.93 [0.33–2.65] and 0.91 [0.71–1.17], respectively), for different comparators, and for the most common types of cancer, when analyzed separately (Fig. 2). Separate analyses on individual malignancies in trials with different comparators were not performed because of the insufficient number of events recorded in each group.

The cumulative incidence density of cancer in the rosiglitazone group was significantly ($P < 0.05$) lower than that in comparators (0.23 [95% CI 0.19–0.26] vs. 0.44 [0.34–0.58] cases/100 patient-years; $P < 0.05$). The pooled rate ratio for rosiglitazone (versus comparators) was 1.02 (95% CI 0.67–1.57).

CONCLUSIONS — Available data from randomized clinical trials, summarized in the present meta-analysis, do not support the recent hypothesis of an increased risk of cancer associated with rosiglitazone (2). On the contrary, the incidence of malignancies in patients receiving rosiglitazone is not higher than that observed with comparators, although a possible protective effect of the drug, as suggested by previous observations, was not confirmed by the present data (1). In consideration of the fact that metformin treatment is associated with reduced risk of cancer in epidemiological studies (18), the hypothesis of a protective effect attributable to enhancement of insulin sensitivity and/or reduction of circulating insulin levels should be considered, along with other more direct, PPAR-γ–dependent or –independent effects of the drug (4,5,19). However, the pooled rate ratio did not highlight any effect of rosiglitazone on the risk of cancer. This discrepancy could be due to the fact that the proportion of subjects receiving rosiglitazone and control treatments varies across trials enrolling patients with different characteristics, which may affect the incidence of cancer. It should also be considered that incidence densities and rate ratios reported in the present analysis were obtained on the basis of several problematic assumptions (i.e., that rates of loss at follow-up, mortality, and incidence of malignancies were constant throughout the duration of each trial); these results should therefore be considered with caution. A meta-analysis of rosiglitazone trials based on patient-level data should be performed to gather more reliable information on this issue.

The gold standard for the assessment of the effects of drug treatments on major outcomes is represented by specifically designed and appropriately sized randomized clinical trials. Unfortunately, in the case of hypoglycemic drugs, such trials are often unavailable. Therefore, meta-analyses of events occurring in randomized trials designed with different end points have been used as a surrogate source of information (15). The limitations of this procedure should be clearly recognized; in particular, the classification of outcomes reported as adverse events and not as predefined end points can be problematic. Notably, most pub-

Table 1—*Main characteristics of clinical trials included in the meta-analysis*

Study (11)*	Characteristics	Comparator	Duration (weeks)	Number R/C	Mean age (years)	Mean A1C (%)	Incident cases of cancer R/C
Nondiabetic subjects							
Trials on GSK Web site							
100684	Metabolic syndrome	Placebo	52	43/47	45	—	0/0
49653/330	Plaque psoriasis	Placebo	52	1,181/382	44	—	3/1
49653/331	Plaque psoriasis	Placebo	52	706/325	45	—	0/1
49653/334	Insulin resistant	Placebo	52	178/177	68	—	4/3
49653/392	Insulin resistant	Metformin	52	16/15	56	—	0/0
49653/131	Insulin resistant	Placebo	26	39,427	48	—	0/0
49653/452	Multiple sclerosis	Placebo	26	26/25	42	—	0/1
ARA102198	Rheumatoid arthritis	Placebo	26	49/49	56	—	0/0
AVA100193	Alzheimer's disease	Placebo	24	394/124	71	—	0/0
Other published trials							
Carr	HIV infection	Placebo	48	53/55	45	—	1/0
Sidhu	Coronary artery disease	Placebo	48	46/46	62	—	0/0
Silic	HIV infection	Metformin	48	30/30	42	—	0/0
van Wijk	HIV infection	Metformin	26	19/20	47	—	0/0
Coll	HIV infection	Metformin	26	15/16	48	—	0/0
Cavalcanti	HIV infection	Placebo	24	48/48	47	—	0/0
Baillargeon	PCOS	Placebo	24	42/30	27	—	0/0
Lemay	PCOS	None	24	15/13	24	—	0/0
Type 2 diabetic patients							
Trials on GSK Web site							
49653/048 (ADOPT)†	Monotherapy	Glyburide	208	1,456/1,441	56	7.3	63/71
49653/048 (ADOPT)†	Monotherapy	Metformin	208	1,456/1,454	57	7.3	63/67
49653/080	Monotherapy	Glyburide	156	104/99	56	9.1	1/3
49653/097	Monotherapy	Glyburide	148	122/120	56	8.9	1/4
49653/135	Combined therapy	Placebo	104	116/111	68	7.4	4/7
49653/211	NYHA-II, mono-combined	Placebo	52	110/114	64	NR	2/3
49653/020	Monotherapy	Glyburide	52	384/203	60	8.2	3/0
AVM100264	Combined therapy	Sulfonylureas	52	294/302	59	8.0	2/1
712753/008	Combined therapy	None	48	284/135	55	NR	3/0
49653/137	Combined therapy	Glyburide	32	204/185	59	8.4	2/4
BRL49653/185	Mono-combined	None	32	563/142	59	7.4	4/2
SB-712753/003	Combined therapy	Placebo	32	254/272	59	7.2	0/1
SB-712753/007†	Monotherapy, OL	Metformin	32	159/154	59	7.2	0/0
SB-712753/007†	Combined therapy, OL	None	32	155/154	59	7.2	0/0
49653/128	Combined therapy	Placebo	28	39/38	58	9.6	0/0
49653/134	Combined therapy	Placebo	28	561/276	55	8.7	0/2
SB-797620/004	Monotherapy	Glimepiride	28	232/225	53	9.0	1/0
49653/024	Monotherapy	Placebo	26	774/185	57	8.9	5/1
49653/044	Combined therapy	Placebo	26	71/34	54	9.6	0/0
49653/079	Monotherapy	Glyburide	26	104/106	58	9.2	1/0
49653/079	Combined therapy	Placebo	26	99/106	58	9.2	2/0
49653/082	Combined therapy	Placebo	26	212/107	56	9.1	0/0
49653/085	Combined therapy	Placebo	26	138/139	61	NR	1/0
49653/093†	Monotherapy	Metformin	26	107/109	59	8.7	0/0
49653/093†	Combined therapy	Placebo	26	106/109	59	8.7	0/0
49653/094	Combined therapy	Placebo	26	232/116	58	8.8	0/0
49653/095	Combined therapy	Placebo	26	196/96	58	9.0	1/0
49653/096	Combined therapy	Placebo	26	232/115	60	9.1	2/0

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Table 1—*Continued*

Study (11)*	Characteristics	Comparator	Duration (weeks)	Number R/C	Mean age (years)	Mean A1C (%)	Incident cases of cancer R/C
49653/109	Monotherapy	Glipizide	26	52/25	53	8.0	0/0
49653/125	Combined therapy, OL	None	26	175/173	56	8.9	0/0
49653/127	Combined therapy	Placebo	26	56/58	60	9.0	0/2
49653/136	Combined therapy	Placebo	26	148/143	65	8.2	2/0
49653/145	Combined therapy	None	26	231/242	61	8.6	1/0
49653/147	Combined therapy	Placebo	26	89/88	54	9.1	0/0
49653/162	Combined therapy	Placebo	26	168/172	60	8.0	2/0
49653/234	Combined therapy	Placebo	26	116/61	63	8.1	1/0
49653/390	Combined therapy	None	26	33/30	NR	NR	1/0
49653/369	Monotherapy	Glyburide	26	25/24	52	6.8	0/0
49653/132	Combined therapy	Placebo	24	442/112	59	9.8	1/1
49653/347	Combined therapy	Placebo	24	418/212	53	9.0	0/1
49653/015	Combined therapy	Placebo	24	395/198	61	9.2	4/0
49653/284	Combined therapy	Placebo	24	382/384	55	8.0	1/0
SB-712753/002	Combined therapy	Placebo	24	288/280	58	7.5	1/0
49653/090	Monotherapy	Placebo	24	228/75	59	8.8	1/0
49653/325	Combined therapy	Placebo	24	196/195	53	8.0	0/1
SB-712753/009	Combined therapy	Placebo	24	162/160	57	8.7	2/0
AVD102209	Combined therapy	Placebo	24	132/131	56	9.6	0/0
49653/143	Combined therapy	Placebo	24	121/124	52	9.2	1/0
49653/207	Children monotherapy	Metformin	24	99/101	14	8.0	0/0
49653/282	Combined therapy	Glyburide	24	69/72	60	7.6	0/0
Other published trials							
Ko	Combined therapy	Insulin	52	56/56	58	9.6	0/0
Derosa (a)	Combined therapy	Glimepiride	52	49/50	53	8.0	0/0
Derosa (b)	Combined therapy	Pioglitazone	52	48/48	55	9.0	0/0
Derosa (c)	Monotherapy	Pioglitazone	52	45/42	54	8.1	0/0
Rahman	Monotherapy	Placebo	52	11/11	47	7.5	0/0
Kelly	Combined therapy	Glyburide	26	20/16	60	7.6	0/0
Reynolds	Monotherapy	Placebo	26	8/10	49	9.2	0/0
Osman	Monotherapy, PTCA	Placebo	26	8/8	55	9.6	0/0
Zhou	Combined therapy	Placebo	24	442/112	56	9.8	0/0
Goldberg	Monotherapy	Pioglitazone	24	369/366	56	7.5	0/0
Weissman	Combined therapy	Placebo	24	358/351	55	8.0	0/0
Agrawal	Combined therapy	None	24	288/280	58	7.5	0/0
Dailey	Combined therapy	Placebo	24	181/184	57	8.1	0/1
Garber	Combined therapy	Glyburide	24	158/160	56	8.5	0/0
Wang	Mono-combined	None	24	35/35	61	7.3	0/0
Wong	Combined therapy	None	24	26/26	62	7.2	0/0
Jung	Combined therapy	Metformin	24	15/15	57	9.1	0/0
Total	—	—	39.2	16,332/12,522	55.3	8.1	124/178

*See APPENDIX for references. †Trials with multiple comparators. ADOPT, A Diabetes Outcome Progression Trial; mono-combined, monotherapy or combined therapy; NR, not reported; NYHA-II, New York Heart Association, Class II; OL, open label; PCOS, polycystic ovary syndrome; PTCA, percutaneous transluminal coronary angioplasty; R/C, rosiglitazone versus comparator.

lished trials do not report any information on incident malignancies; cases could be easily identified only in trials reported on the GSK Web site (11), which contains a detailed description of all serious adverse events. Furthermore, the inclusion in a meta-analysis of many small trials with a very low number of events poses challenging problems in statistical analysis (12–14). It should also be considered that clinical trials usually enroll relatively young patients with low comorbidity and high compliance, who can be considered to have a low risk for cancer.

On the other hand, a trial assessing the effect of a hypoglycemic drug on the incidence of malignancies would be hypothetically very difficult to realize because of the required sample size and duration of follow-up. For this reason, information on this end point can be obtained only through epidemiological studies or meta-analyses of trials designed for other purposes. The epidemiological

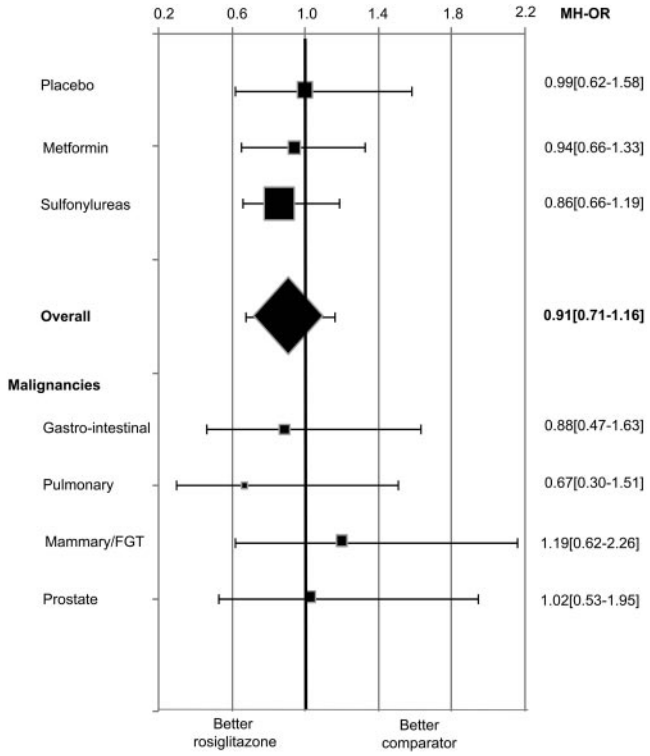

Figure 2—*Effects of rosiglitazone on incident malignancies. The size of the data markers represents the relative weight of the trial according to the number of incident cancers. FGT, female genital tract.*

approach provides the advantage of the possibility of collecting large samples with a long duration of follow-up; however, in observational studies multiple adjustments for confounders can never fully eliminate the prescription bias (i.e., the effect of differences in characteristics of patients on different therapeutic choices). Such a bias could be responsible for the discrepancy between our results and those of a recent cross-sectional survey (2).

The number of events included in the present meta-analysis does not allow a reliable analysis on specific types of cancer. However, our data are consistent with the possibility of specific protection from lung cancer, which has been reported previously in a epidemiological study (1). Considering that the pathogenesis of different forms of cancer is very heterogeneous, the drug could have divergent effects on different malignancies. Interestingly, no reduction of risk for cancer of the female genital tract was detected in rosiglitazone-treated patients, although the drug is used in the treatment of polycystic ovary syndrome (20), which is a known risk factor for these malignancies (21). Larger databases are needed to elucidate the risk profile for individual forms of cancer in rosiglitazone-treated patients.

In summary, the use of rosiglitazone appears to be safe with respect to risk of incident malignancies, whereas further studies are needed to confirm a possible protective effect. The incidence of cancer, which can probably be modified by hypoglycemic drugs, deserves to be considered among the relevant outcomes for the choice of treatment for type 2 diabetes.

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