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EXTENDED REPORT

Safety profile of protein kinase inhibitors in rheumatoid arthritis: systematic review and meta-analysis

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Handling editor Tore K Kvien

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2012-203116).

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Accepted 17 March 2013
Published Online First 18 April 2013

To cite: Salgado E, Maneiro JR, Carmona L, *et al*. *Ann Rheum Dis* 2014;**73**:871–882.

ABSTRACT

Objective To summarise the adverse events (AE) reported in patients with rheumatoid arthritis (RA) treated with protein kinase inhibitors (PKi), and identify family and molecule-related AEs.

Methods Systematic review of the PKi used in clinical trials (CTs) in RA. Medline, Embase, Cochrane Library, Web of Knowledge, and international abstracts of congress were reviewed, (up to 31 October 2012). Search was limited to interventional studies of PKi used in CTs in RA, written in English, and reporting frequencies of AE. Diseases with similar comorbidity burden also were included. Frequency of AE, serious AE (SAE), death and discontinuation due to AEs (DCAE) were recorded. Risk of bias was assessed. Meta-analysis was carried using pooled relative risk (RR) with 95% CI as effect measure.

Results The search produced 4410 hits. Forty-one articles reporting data on 21 PKi of the Janus kinase (JAK), SYK, p38 and cKit families were selected for detailed analysis. In patients treated with p38 inhibitors, RR for dizziness was 2.36 (1.20 to 4.63), and in patients treated with c-Kit inhibitors, RR for oedema was 3.43 (1.58 to 7.42). In patients treated with the JAK inhibitor tofacitinib, RR for hypercholesterolaemia was 1.70 (1.10 to 2.63) that was dose related. In patients treated with the Syk inhibitor fostamatinib, pooled RR for hypertransaminasaemia, hypertension, diarrhoea and neutropenia were 2.93 (1.02 to 8.43), 2.80 (1.58 to 5.99), 5.20 (3.19 to 8.49) and 9.24 (2.22 to 38.42), respectively. Serious infections and malignancies were not significantly more frequent in PKi-treated patients than in comparator groups.

Conclusions Event rates of serious infections and malignancies with PKi are not different from biologics. In addition, PKi have a unique safety profile related to target and off-target inhibition of kinases, at times dose related.

INTRODUCTION

Treatment of rheumatoid arthritis (RA) has changed significantly with the arrival of biologic therapies. Biologics are highly selective and efficacious. However, they have the potential to induce immunogenicity as foreign protein. In addition, biologics need special transport and storage conditions, are handled under restricted conditions, and their cost of acquisition is high. Small molecules that block intracellular cytokine signalling pathways represent an alternative pharmacological approach to biologic therapies as a means of selectively inhibiting molecules important in the pathogenesis of disease. They are easy to synthesise and can be administered orally. Protein kinases (PK) are important enzymes in cell signalling. The PK inhibitors (PKi) of the p-38, Janus kinase (JAK), SyK, and c-Kit-activated kinases have been tested in clinical trials (CTs) in RA. PKs can be divided into 10 groups based on function and the amino acid sequence similarities, presence of accessory domains and modes of regulation. All PKs are assigned to a group, which consists of many families and multiple subfamilies.[1] Mitogen-activated protein kinases (MAPK) are intracellular enzymes related to gene transcription.[2] They are three different families; extracellular signal-regulated kinases, c-JUN N-terminal kinase, and p38 MAPK. p38 belongs to the family of stress-activated PK included in the serine/threonine PK group.[3] The p38α isoform plays a key role in the regulation of proinflammatory cytokine production.[4] BMS-582949, dilmapimod, doramapimod, pamapimod, talmapimod, VX-702 and VX-745 are highly selective third-generation inhibitors of p38.[5] JAKs play important roles in innate and adaptive immune responses. Cytokine receptors containing the common γ-chain subunit that are relevant for cytokines participating in RA signal through JAK1 and JAK3. JAKs belong to the receptor-associated tyrosine kinases family of the tyrosine PK group.[6] Tofacitinib is a pan-JAK inhibitor, baricitinib inhibits JAK1 and JAK2, GLPG-0634 JAK1, and vx-509 JAK3.[7–9] c-Kit receptor (c-kit, CD117) is a transmembrane glycoprotein and member of the receptor tyrosine kinase subclass III family.[10]C-Kit, and its ligand, the stem cell factor (steel factor, or mast cell growth factor[11–14]), are essential for the growth and survival of human mast cells that may have a role in the pathogenesis of RA.[15] Imatinib abrogate c-Kit signalling.[16] Also, imatinib attenuates platelet-derived growth factor receptor (PDGFR) signalling in fibroblast-like synoviocytes derived from human patients with RA.[17] Masitinib inhibits c-Kit, PDGFR, the intracellular kinase Lyn, and to a lesser extent fibroblast growth factor receptor 3 signalling.[18] The tyrosine kinase Syk is a member of a non-receptor cytoplasmic tyrosine kinases family of tyrosine kinases group. It is a critical molecule in B cells and cells expressing Fc-activating receptors.[19] Fosfamatinib is a Syk signalling inhibitor. PKi modulates the release of inflammatory mediators, and treatment with PKi is an attractive strategy for the treatment of inflammatory conditions. Most PKi bind competitively to a conserved adenosine-5´-triphosphate (ATP) binding pocket,

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and may cross-react with different kinases within and outside that family and other ATP binding proteins (off-target inhibition).[20] Off-target and specific target-related adverse events (AE) need to be recognised. There is a large experience of treatment with PKi in cancer. In cancer, broad-spectrum low affinity binding to multiple targets leads to a collective effect on efficacy and safety.[21] As an example, sunitinib is a multitargeted tyroxine kinase inhibitor. Dose-dependent off-target inhibition of the multitargeted tyroxine kinase inhibitor PK sunitinib contributes to its cardiotoxicity.[22 23] Kinome-wide profiling has emerged as an important strategy in compound safety. The objective of this study is to summarise the safety knowledge of PKi used in CTs in RA, and to sort out class from molecule-related AEs. Efficacy was not a consideration in our study; instead, analysis of safety profile of several PKi was done to identify molecule and family related target and off-target AE. Inhibition of p38 has limited efficacy in RA. Several explanations have been offered. They include upregulation of enzymes proximal or distal in p38 pathway or in as-yet unidentified upregulation of one or more factors in other inflammatory pathway.[24] Also, dosing, biodistribution, targeting of the wrong p38 kinase isoforms, and compensatory effects in other kinases that can regulate the same genes have been proposed.[25] Nevertheless, upstream inhibition of the p38 MAPK signalling pathway is feasible and efficacious in animal models of arthritis.[26] Thus, information regarding safety of p38 inhibition may be relevant if this preclinical information leads to the development of upstream inhibitors of the p38 signalling pathway. All in all, this knowledge would potentially contribute to the safety profiling of the emerging PKi drugs, and for conceiving safer drugs.

METHODS

A systematic literature review was conducted to identify all safety data from published CT of the PKi used in RA. The selected PKi were AMG-548, ARRY-371797, BMS-582949, dilmapimod, doramapimod, pamapimod, PH-797804, SCIO-323, talmapimod, VX-702, VX-745, GLPG-0634, baricitinib, ruxolitinib, tofacitinib, VX-509, imatinib, masitinib, fostamatinib and ARRY-438162.

Data sources

We identified randomised controlled trials, but also incorporated studies without comparator arm and open trials including more than 10 patients. Trials must have durations longer than 2 weeks to ensure occurrence of enough AEs, and provide safety information extractable as AE rate. Studies on healthy individuals, patients with RA, and patients with diseases other than RA with similar comorbidity burden were included. Studies on patients with malignancies, intensive care pathologies, graft versus host disease, transplantation, with impaired renal or hepatic function, hypereosinophilic syndrome, Langerhans histiocytosis and myelodysplastic syndromes, and studies on pharmacological interaction of PKi with other drugs were excluded.

The protocol of this review is available by email upon request. PRISMA consensus was followed for reporting the results of the review and meta-analysis.[27]

Search strategy

Medline, Embase, Cochrane Library and Web of Knowledge were searched for articles published from 2000 to October 2012. Abstracts from the American College of Rheumatology from 2006, and European League Against Rheumatism from 2001, and Advisory Committee Meeting on tofacitinib for the treatment of RA briefing document 9 May 2012[28] were also reviewed. Search strategy comprised all possible typing names of each PKi as free terms (see online supplementary figure S1). Terms of population, design and comparator were not included. Search was limited to publications in the English language.

Study selection

Screening of articles by title and abstracts was performed by two reviewers (ES and JRM). Discordant items were selected through a third reviewer (LC). Subsequently, complete reading of articles was performed, and those meeting the inclusion criteria were selected. Additional articles were found by hand search, and reviewing the references in the selected studies.

Data extraction

Publication details, characteristics of patients, concomitant medication and exposure time were collected. AE were recorded using the preferred Medical Dictionary for Regulatory Activities (MedDRA) term. When rate of the AE was reported in the control group, this data was also recorded. To simplify the analysis, dizziness and vertigo were recorded as 'dizziness' and nausea, and vomiting as 'nausea'. Rate of serious AEs (SAE), discontinuation due to AEs (DCAE), and deaths were also recorded.

Risk of bias

We created an ad hoc checklist (available upon request) based on the recommendations of The Cochrane Collaboration to evaluate risk of bias of the included studies.[29] Score goes from 0% to 100%, being 100 equal to absence of risk of bias. Level of evidence of each study was evaluated using the OCEBM Levels of Evidence Working Group.[30]

Statistical analysis

To summarise AEs occurring during treatment with PKi, incidence rate (IR) of events occurring in at least 10% of patients was compared with the AEs in the comparator group, and reported as IR ratio. Data from AEs were pooled if stratified by dose or treatment schedules. Difference of IR was reported when rate in comparator group was null.

Meta-analyses were performed when at least three studies of the same PKi molecule or the same PKi family had comparable outcome measures, by using a random-effects approach and computing relative risk (RR).[31] Study effects were plotted against the inverse of their SEs to identify risk of publication bias, which was assessed visually by funnel plots symmetry and statistically by Egger test.[32] Heterogeneity was tested using I^2.[33 34] An I^2 value >40% was arbitrarily taken as high heterogeneity. When heterogeneity was present, possible causes were investigated using sensitivity analysis and metaregression. Metaregression aimed to determine the contribution of time of exposure to PKi, underlying disease, use of concomitant methotrexate (MTX), quality of the data and level of evidence to heterogeneity. A $p<0.05$ was considered significant in all the analyses, but in metaregression where 0.10 was the significance level. Sensitivity analysis was performed including only studies with full report on patients with RA with at least 12 weeks of exposure to tofacitinib and fostamatinib. Stata V.11.1 (Stata/IC 11.1 for Windows, StataCorp LP, Texas, USA) was used in all statistical analyses.

RESULTS

The search produced 4410 hits. Sixty-three articles were selected for complete reading after discharging duplicates, and exclusion by title and abstract screen. Twenty-two items were excluded after review (see online supplementary table S1), and

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Table 1 Characteristics of the selected studies

Author, country	PKi (target)	Study design	Time*	N	Disease	Age†	Female (%)‡	Outcomes	Quality (%)	LE
Genovese[52] USA	BMS-582949 (p38)	CT phase 2, RD, DB, placebo-controlled, all with MTX	12	121	RA	–	–	AE, SAE and DCAE	73	1b
Wang[53] USA	BMS-582949 (p38)	CT phase 1, RD, DB, placebo-controlled	4	33	RA	–	–	AE, SAE and DCAE	73	2b
Anand[36] UK	Dilmapimod (p38)	CT, pilot study, RD, DB, placebo-controlled, some treatments for pain allowed	2	47	Neuropathic pain	55.1 (22–78)	48	AE and SAE	93	2b
Schreiber[54] Germany	Doramapimod (p38)	CT phase 2, RD, DB, placebo-controlled	8	284	CD	36.0 (27–45), median (p25–p75)	57	AE and SAE	90	1b
Alten[55] Germany	Pamapimod (p38)	CT phase 2, multicentric, DB, RD, placebo-controlled, all with MTX, antipaludics allowed	12	327	RA	–	–	AE, SAE and DCAE	73	1b
Cohen [42] USA	Pamapimod (p38)	CT phase 2, RD, DB, MTX-controlled	12	204	RA	47.3±12.4 vs 50.7±12.2	83 vs 85	AE, SAE and DCAE	93	1b
Genovese [56] USA	Talmapimod (p38)	CT phase 2, RD, DB, placebo-controlled	13	301	RA	54.3±12.8	80	AE, SAE and DCAE	97	1b
Damjanov [57] Serbia	VX-702 (p38)	Study 304: CT phase 2, RD, DB, placebo controlled, all with MTX	12	117	RA	55±7.4 vs 55.4±9.1	73 vs 76	AE, SAE and DCAE	87	1b
Damjanov [57] Serbia	VX-702 (p38)	Study VERA :CT phase 2, RD, DB, placebo controlled, SSZ and antipaludics allowed	12 (16)	313	RA	55±10.5 vs 53±11.7	81 vs 82	AE, SAE and DCAE	87	1b
Allaart[58] Netherlands	VX-745 (p38)	CT, pilot study, parallel group, uncontrolled	4	12	RA	60	92	AE, SAE and DCAE	50	2b
Weisman[59] USA	VX-745 (p38)	CT phase 2 ,RD, DB, placebo-controlled	12	59	RA	Median 55	83	AE, SAE and DCAE	73	2b
Vanhoutte [48] Belgium	GLPG-0634 (JAK)	CT, phase 2a, RD, DB, placebo-controlled, all with MTX	4	36	RA	–	92	AE, SAE and DCAE	68	2b
Greenwald [60] USA	Baricitinib (JAK)	CT phase 2, RD, DB, placebo-controlled, all with DMARD	12	125	RA	(54–58)	80	AE, SAE and DCAE	73	1b
Keystone [9] USA	Baricitinib (JAK)	CT, phase2b, RD, DB, placebo-controlled, all with MTX	24	301	RA	51	83	AE, SAE and DCAE	64	1b
Boy [61] USA	Tofacitinib (JAK)	CT phase 1, RD, DB, placebo controlled	2	58	Psoriasis	(23–69)	–	AE, SAE and DCAE	73	2b
Burmester [62] Germany	Tofacitinib (JAK)	CT, phase 3, RD, DB, placebo-controlled, all with MTX	24 (12)	399	RA	(54.3–55.4)	–	AE, SAE and DCAE	50	1b
Cohen [63] USA	Tofacitinib (JAK)	CT phase 1, single-arm, open-label, all with MTX	4	12	RA	–	–	AE, SAE and DCAE	62	2b
Fleischmann [38] USA	Tofacitinib (JAK)	CT phase 2, RD, DB, placebo-controlled, adalimumab-controlled, antipaludics allowed	24	306	RA	53±13.7 vs 53.7±12.5	88 vs 86	AE, SAE and DCAE	90	1b
Kremer [64] USA	Tofacitinib (JAK)	CT, phase 3, RD, DB, placebo-controlled, all with at least one DMARD	24	792	RA	(50.8–53.3)	–	AE and SAE	60	1b
Kremer [44] USA	Tofacitinib (JAK)	CT phase 2, RD, DB, placebo-controlled	6	264	RA	51.3±12.1 vs 50.4±11.5	85 vs 86	AE and SAE	87	1b
Kremer (2011)[37] USA	Tofacitinib (JAK)	CT phase 2, RD, DB, placebo-controlled, all with MTX	24	493	RA	53±13.4 vs 53.3±11.8	81 vs 80	AE, SAE and DCAE	90	1b
Tanaka [39] Japan	Tofacitinib (JAK)	CT phase 2, RD, DB, placebo-controlled, all with MTX	12	136	RA	50.6±12.4 vs 51.5±10.3	85	AE and DCAE	90	1b
Tanaka Mono [65] Japan	Tofacitinib (JAK)	CT phase 2b, RD, DB, placebo-controlled	12	317	RA	(52.6–54.7)	–	AE, SAE and DCAE	64	1b
	Tofacitinib (JAK)		48 (12)	797	RA	–	–	AE, SAE and DCAE	62	1b

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Table 1 Continued

Author, country	PKi (target)	Study design	Time*	N	Disease	Age†	Female (%)‡	Outcomes	Quality (%)	LE
van der Heijde [66] Netherlands		CT phase 3, RD, DB, placebo-controlled, all with MTX								
van Vollenhoven [40] USA Sweden	Tofacitinib (JAK)	CT phase 3, RD, DB, placebo and adalimumab-controlled, all with MTX	48	513	RA	52.95±1.9 vs 53.73±13.7	75 vs 86	AE, SAE and DCAE	93	1b
Fleischmann [41]	Tofacitinib (JAK)	CT phase 3, RD, DB, placebo controlled, monotherapy	24	611	RA	(49.7–52.4)	87	AE, SAE and DCAE	80	1b
Sandborn [67] USA	Tofacitinib (JAK)	CT phase 2, RD, DB, placebo-controlled, monotherapy	8	194	Ulcerative colitis	42.5±14.7 vs 42.5±10.2	43	AE, SAE and DCAE	80	1b
Papp[68] Canada	Tofacitinib (JAK)	CT phase 2, RD, DB, placebo-controlled, monotherapy	12	197	Psoriasis	43,9±13,0 vs 44,43±14	28% vs 39%	AE, SAE and DCAE	80	1b
Fleischmann [69] USA	VX-509 (JAK)	CT phase 2b, RD, DB, placebo-controlled, monotherapy	12	204	RA	56.1	81	AE and SAE	54	1b
Daniels [70] USA	Imatinib (cKit)	CT phase 2,RD, DB, placebo-controlled	96	119	IPF	67.8 (52–79) vs 66 (47–79)	36 vs 22	AE and SAE	83	2b
Ghofrani [71] Germany	Imatinib (cKit)	CT phase 2, RD, DB, placebo-controlled	24	59	Pulmonary HT	44.2±15.7 vs 44.4±15.3	71 vs 64	AE, SAE and DCAE	83	2b
Khanna [72] USA	Imatinib (cKit)	CT Phase 1–2, single arm, open label	48	20	ILD in SSc	46.1±14.2	65	AE, SAE and DCAE	62	2b
Spiera [73] USA	Imatinib (cKit)	CT phase 2, single arm, open label	48	30	dcSSc	48 (18–71), median (range)	18	AE, SAE and DCAE	69	2b
Humbert [74] France	Masitinib (cKit)	CT phase 2, RD, DB, placebo-controlled	16	44	Asthma	53±13	71	AE, SAE and DCAE	73	2b
Piette [75] France	Masitinib (cKit)	CT phase 2, RD, DB, placebo-controlled, all with cholinesterase inhibitors	24	34	Alzheimer disease	78±11 vs 72±12	75 vs 58	AE, SAE and DCAE	90	2b
Tebib [76] France	Masitinib (cKit)	CT phase 2, open-label, uncontrolled	12	43	RA	54.7±10.8 (27–75)	78	AE, SAE and DCAE	73	2b
Vermersch [77] France	Masitinib (cKit)	CT phase 2a, RD, DB, placebo controlled	48	35	Multiple sclerosis	48±8	51%	AE, SAE and DCAE	87	2b
Genovese [78] USA	Fostamatinib (SyK)	CT Phase 2, RD, DB, placebo-controlled	12	219	RA	56 (22–79) vs 56 (18–82)	81 vs 80	AE, SAE and DCAE	77	1b
Podolanczuk [79] USA	Fostamatinib (SyK)	CT phase 2, open-label, single arm	36	16	ITP	66 (31–81), median (range)	62	AE and SAE	62	2b
Weinblatt [80] USA	Fostamatinib (SyK)	CT phase 2, RD, DB, placebo-controlled, all with MTX	12	189	RA	54.3 (28–71) vs 52.1(20–75)	89 vs 86	AE SAE	90	1b
Weinblatt [81] USA	Fostamatinib (SyK)	CT phase 2, RD, DB, placebo-controlled, all with MTX	24	457	RA	52.4 (24–83) vs 51.5 (18–87)	86 vs 85	AE, SAE and DCAE	90	1b
Briefing document of Advisory Committee Meeting[28]	Tofacitinib (Jak)	Pooled analysis from phase 2, phase 3 and Long term extension studies	–	P2 1369 P3 3030 LTE 3515	RA	–	–	Only OI deaths and MLG	60	1b
Kavanaugh [35] USA	Fostamatinib (SyK)	Pooled analysis from TASKI1, TASKI2, TASKI3, TASKI1 extension study and open label study study (C-935788-012).	96	1076	RA	–	–	Only OI deaths and MLG	70	1b[i]

*Exposure time of treatment (time for safety assessment).
†Age expressed as mean±SD (range) if other measure is not explicated; for global patients or 'control group versus treated group'.
‡Sex expressed as female percentage; for global or 'control group versus treated group'.
AE, adverse events; CD, Crohn's disease; CT, clinical trial; DB, double-blind; dcSS, diffuse cutaneous systemic sclerosis; DCAE, discontinuation adverse events; DMARD, disease modifying antirheumatic drugs; HT, hypertension; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; ITP, immune thrombocytopenic purpura; JAK, Janus kinase; LE, level of evidence; LTE, long term extension; MLG, malignancies; Mono, monotheraphy; MTX, methotrexate; OI, opportunistic infections; P2, phase 2; P3, phase3; PKi, protein kinase inhibitor; RA, rheumatoid arthritis; RD, randomised; SAE, serious adverse events; SSc, systemic sclerosis; SSZ, sulfasalazine.

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Table 2 Comparison of the incidence rates (IR) of adverse events (AE) by protein kinase inhibitor (PKi) in treated patients and comparator arms

PKi	Primary targets	SAE	DCAE	Dizziness	Rash	Hypertransaminasemia	Nausea	Diarrhoea	Others
BMS-582949	p38-α	0.37 (0.35;2.26) 0.36 (0.08;1.65)*	1.54 (0.30;9.93) 1.11 (0.21;5.80)*						
Dilmapimod	p38-α	0.11 (0.00;0.81) 0.11 (0.01;0.89)*	1.02 (0.07;14.1) 1.02 (0.14;7.25)*				1.02 (0.07;14.1) 1.02 (0.14;7.25)*	0.51 (0.01;9.82) 0.51 (0.05;5.64)*	Headache 1.27 (0.45;3.73)/1.27 (0.50;3.24)*
Doramapimod	p38-α	0.61 (0.21;1.94) 0.61 (0.23;1.59)*		1.40 (0.16;66.05) 1.40 (0.16;11.95)*	0.70 (0.11;7.33) 0.70 (0.14;3.60)*	5.03 (0.79;209.45) 5.03 (0.67;37.66)*	0.48 (0.17;1.44) 0.48 (0.19;1.21)*	0.14 (0.02;0.26)†	Headache 0.74 (0.28;2.32)/0.74 (0.29;1.90)*
Pamapimod	p38-α	1.16 (0.47;3.43) 1.28 (0.52;3.10)*	1.79 (0.76;5.14) 1.88 (0.79;4.47)*	2.70 (1.18;7.63) 2.55 (1.09;5.97)*		0.80 (0.37;1.93) 0.84 (0.39;1.81)*	0.69 (0.29;1.78) 0.66 (0.28;1.55)*	5.23 (0.84;216.6) 5.39 (0.66;43.92)*	Hematuria 1.84 (0.62;7.38)/1.84 (0.63;5.37)* CPK increased 1.25 (0.35;6.72)/1.27 (0.34;4.75)*
Talmapimod	p38-α	0.90 (0.22;5.27) 0.90 (0.24;3.40)*	1.62 (0.60;5.44) 1.62 (0.61;4.25)*	2.36 (0.54;21.44) 2.36 (0.54;10.40)*	5.24 (1.33;45.15) 5.24 (1.25;21.88)*	0.02 (–0.02; 0.05)†	0.96 (0.36;2.96) 0.96 (0.38;2.43)*	0.74 (0.24;2.73) 0.74 (0.26;2.14)*	
VX-702	p38-α	1.45 (0.50;5.16) 1.46 (0.52;4.10)*	2.60 (0.55;24.38) 2.60 (0.56;11.90)*			1.90 (0.50;10.63) 1.88 (0.52;6.73) *		4.16 (0.56;184.39) 4.18 (0.51;34.10)*	Proteinuria 1.45 (0.50;5.16)/1.43 (0.52;3.98)* Neutrophilia 0.73 (0.20;2.90)/0.72 (0.23;2.26)*
VX-745	p38-α					0.55 (0.11;0.98) †			
GLPG-0634	JAK1		0 (0;0)†						
Baricitinib	JAK1 JAK2	0.97 (0.14;10.67) 0.97 (0.18;5.27)*						0.55 (0.11;3.54) 0.55 (0.13;2.30)*	Headache 1.65 (0.35;15.48)/1.65 (0.36;7.52)*
Tofacitinib	JAK1 JAK2 JAK3	0.85 (0.59;1.26) 0.83 (0.57;1.21)*	1.08 (0.74;1.63) 1.15 (0.78;1.69)*	0.94 (0.38;2.77) 0.97 (0.39;2.38)*	2.35 (0.57;20.67) 2.02 (0.45;8.50)*	1.40 (0.59;4.05) 1.25 (0.53;2.94)*	0.52 (0.33;0.84) 1.43 (0.67;3.07)*	1.87 (0.86;4.85) 1.57 (0.69;3.53)*	Headache 2.90 (1.48;6.48)/2.19 (1.09;4.37)* Blood creatinine increase 4.77 (1.58;23.58)/ 4.57 (1.49;13.98)* Anemia 1.60 (0.68;4.59)/1.47 (0.61;3.55)* Hypercholesterolaemia 2.42 (1.45;4.33)/1.91 (1.15;3.18)* Hypertension 0.86 (0.39;2.15)/0.80 (0.38;1.73)*
VX-509	JAK3	2.01 (0.27;89.29) 2.01 (0.25;16.09)*	1.63 (0.37;14.90) 1.63 (0.37;7.25)*			1.26 (0.27;11.8) 1.26 (0.28;5.74)*			
Imatinib	ABL1 c-Kit PDGFR	1.60 (0.99;2.66) 1.17 (0.69;1.98)*	1.83 (0.94;3.80) 1.79 (0.90;3.56)*	1.06 (0.09;55.48) 1.11 (0.07;17.70)*	2.86 (1.29;7.18) 3.31 (1.50;7.30)*	1.33 (0.66;2.77) 1.60 (0.82;3.12)*	5.79 (2.90;13.12) 3.05 (1.43;6.49)*	2.53 (1.34;5.10) 2.50 (1.31;4.77)*	Oedema 7.57 (3.28;21.43)/3.78 (1.54;9.26)* Fatigue 2.5 (1.29;5.22)/1.44 (0.69;3.02)* Anaemia 6.79 (2.44;26.18)/5.85 (2.02;16.90)* Headache 7.25 (2.22;37.42)/6.58 (1.97;21.94)*
Masitinib	c-Kit PDGFR LynB	2.68 (0.97;10.26) 2.50 (0.88;7.06)*	0.50 (0.33;0.68)†		0.57 (0.38;0.76)†	0.12 (–0.02;0.27)†	0.60 (0.41;0.79)†	0.37 (0.22;0.53)†	Oedema 0.49 (0.32;0.66)† Pruritus 0.13 (0.02;0.25)†
Fostamatinib	SyK	0.14 (0.17;0.26)†	1.57 (0.50;7.95) 2.53 (0.76;8.40)*	2.65 (0.91;10.52) 2.34 (0.79;6.88)*	0.25 (0.09;0.42)†	4.06 (1.25;20.92) 3.80 (1.12;12.94)*	1.67 (0.78;3.99) 1.52 (0.71;3.22)*	2.93 (1.72;5.32) 2.67 (1.58;4.52)*	Headache 1.51 (0.82;2.98)/1.40 (0.77;2.55)* Neutropenia 19.97 (3.39;807.26)/18.54 (2.42;142.09)* Oedema 1.99 (0.24;91.35)/1.99 (0.24;16.50)* Hypercholesterolaemia 0 (0;0)† Hypertension 2.86 (1.54;5.77)/2.92 (1.58;5.40)*

*Incidence rate ratio (IRR) crude/IRR adjusted by study.
†Incidence rate difference in treated patients to kinase inhibitor less in untreated patients.
CPK, creatinine phosphokinase; DCAE, discontinuation due to adverse event; JAK, Janus kinase; PDGFR, platelet-derived growth factor receptor; PKi, protein kinase inhibitor; SAE, serious adverse events.

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41 articles were selected for detailed analysis. In addition, the Briefing document of Advisory Committee Meeting on tofacitinib was included. Flow-chart of selected and excluded studies is available in online supplementary figure S2.

Characteristics of selected studies

Selected publications were phases 2 and 3 CT, and two pooled analyses. Patients numbering 11 858 were included. A total of 11 studies provided data on the p38 inhibitors (BMS-582949, dilmapimod, doramapimod, pamapimod, talmapimod, VX-702 and VX-745), 18 on JAK inhibitors (baricitinib, GLPG-0634, ruxolitinib, tofacitinib and VX-509), 8 on cKit inhibitors (imatinib or masitinib) and 4 on the Syk inhibitor fostamatinib. No studies of mitogen-activated protein kinase kinase (MEK) inhibitors fulfilled entry criteria. One publication was a pooled analysis for tofacitinib,[28] and another a pooled analysis for fostamatinib.[35] Thirty studies concerned patients with RA, and 13 diseases other than RA. Quality of the data was ≥70% in 30 studies. The level of evidence was 1b in 27 studies, and 2b in 16. Table 1 describes the characteristics of studies. Results of the pooled analyses in tofacitinib and fostamatinib in RA-treated patients are shown for opportunistic infections, deaths and malignancies (see online supplementary tables S5, S6 and S7).

Safety of p38 inhibitors

IR of dizziness in pamapimod patients, and IR of rash in talmapimod-treated patients were higher than their comparator groups. Diarrhoea was reported in doramapimod patients, and hypertransaminasaemia in VX-745-treated patients but not in their comparator groups (table 2). SAEs were numerically more common in the comparator group than in dilmapimod treated patients, although exposure was limited.

Eight AEs were meta-analysed to summarise the safety of the p38 (tables 3). Only RR for dizziness was significant (2.36 (CI 1.20 to 4.63)) without heterogeneity (I^2 of 0%, p = 0.956) or publication bias in the funnel-plot (Egger test, p = 0.127) (figure 1). Meta-analysis could not be done to identify molecule-related AEs because of the small number of trials per molecule.

Safety of JAK inhibitors

IR of blood creatinine elevation, headache and hypercholesterolaemia were higher in tofacitinib-treated patients than in the comparator groups (table 2). IR (95% CI) per 100 patients-year (pt-yr) of opportunistic infections was 1.60 (0.194 to 5.780 CI) in baricitininb trials, and 0.43 (0.254 to 0.673 CI) in tofacitinib long-term extension studies. Twelve cases of tuberculosis (IR, 0.113 (0.047 to 0.272 CI) per 100 pt-yr) occurred in tofacitinib-treated patients, and no cases in the comparator groups. Eleven of these cases were identified in countries with high overall rates of tuberculosis. IR of herpes zoster was 4.315 (3.845 to 4.844 CI) in phase 2, phase 3 and long-term extension studies. Standardised incidence rate (SIR) of malignancies (excluding non-melanoma skin cancer) in tofacitinib-treated patients with moderate and severe RA was no superior than expected in the population; SIR of malignancies in tofacitinib-

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Table 3 Results of meta-analyses with relative risks (95% CI)

	Family effect			Molecule-related		
Adverse event	**p38 Kinh**	**JAK Kinh**	**cKit Kinh**	**Fostamatinib (Syk)**	**Tofacitinib (JAK)**	**Masitinib(cKit)**
Death	–	1.06 (0.30–3.63)*	–	–	1.01 (0.026–3.92)	–
SAE	1.23 (0.80–1.89)†	0.93 (0.66–1.30)‡	1.43 (0.97–2.11)	–	0.89 (0.62–1.28)	2.40 (1.03–5.59)
DCAE	1.67 (1.00–2.79)§	1.27 (0.87–1.72)*	2.18 (1.21–3.91)	–	1.20 (0.85–1.70)	4.34 (0.87–21.66)¶
Dizziness	2.36 (1.20–4.63)**	–	–	–	0.97 (0.39–2.36)	–
Rash	–	–	–	–	1.42 (0.43–4.73)	–
Hypertransaminasemia	1.52 (0.86–2.67)††	1.20 (0.54–2.64)‡‡	1.73 (0.99–2.99)	2.93 (1.02–8.43)	1.37 (0.54–3.52)§§	–
Hypercholesterolaemia	–		–	–	1.70 (1.10–2.63)	–
Hypertension	–	–	–	2.80 (1.58–4.99)	0.78 (0.37–1.66)	–
Nausea	0.72 (0.46–1.11)¶¶	–	–	–	1.28 (0.73–2.26)	–
Diarrhoea	1.63 (0.83–3.19)†	1.17 (0.61–2.24)***	–	5.20 (3.19–8.49)	1.24 (0.61–2.54)	–
Headache	0.95 (0.58–1.57)†††	–	–	–	–	–
Blood creatinine increase	–	–	–	–	3.26 (0.84–12.60)‡‡‡	–
Anemia	–	–	–	–	0.88 (0.55–1.42)	–
Oedema	–	–	3.43 (1.58–7.42)	–	–	–
Neutropenia	–	–	–	9.24 (2.22–38.42)	–	–
Opportunistic infections	–	0.57 (0.16–1.99)‡	–	–	–	–
SIAE	1.51 (0.50–4.60)§§§	1.68 (0.71–3.91)*	–	1.07 (0.40–2.91)	1.57 (0.65–3.82)	–

*This meta-analysis included studies with tofacitinib and vx-509.
†This meta-analysis included studies with BMS-582949, dilmapimod, doramapimod, pamapimod, talmapimod and VX-702.
‡This meta-analysis included studies with LY309104, tofacitinib and vx-509.
§This meta-analysis included studies with BMS-582949, dilmapimod, pamapimod, talmapimod and VX-702.
¶There is publication bias (Egger test, p=0.041).
**This meta-analysis included studies with doramapimod, pamapimod and talmapimod.
††This meta-analysis included studies with doramapimod, pamapimod, talmapimod, VX-702 and VX-745.
‡‡This meta-analyis included studies with tofacitinib and vx-509. Studies in Japanese population were excluded.
§§Studies in Japanese population were excluded.
¶¶This meta-analysis included studies with dilmapimod, doramapimod, pamapimod and talmapimod.
***This meta-analysis included studies with tofacitinib and LY309104.
†††This meta-analysis included studies with dilmapimod, doramapimod and pamapimod.
‡‡‡Heterogeneity was I^2=43.6%. Any sources of heterogeneity were identified.
§§§This meta-analysis included studies with dilmapimod, talmapimod and VX-702.
DCAE, discontinuation due to adverse event; JAK, Janus kinase; SAE, serious adverse events.

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Table 4 Sensitivity analysis of the meta-analyses of tofacitinib including only full-reports of rheumatoid arthritis trials with at least 12 weeks of follow-up

Adverse event	Relative risk (95% CI)
Death	0.50 (0.08–3.11)
SAE	1.13 (0.60–2.14)*
DCAE	1.13 (0.65–1.98)
Dizziness	–
Rash	1.25 (0.33–4.73)
Hypertransaminasemia	1.45 (0.51–4.10)†
Hypercholesterolaemia	1.70 (1.01–2.83)
Hypertension	0.78 (0.34–1.66)
Nausea	1.30 (0.65–2.62)
Diarrhoea	1.76 (0.74–4.18)
Headache	–
Blood creatinine increase	–
Anemia	1.01 (0.57–1.82)‡
Oedema	–
Neutropenia	–
Opportunistic infections	–
SIAE	1.06 (0.32–3.56)

*Heterogenety was I^2=64.9%. Concomitant methotrexate was identified as a source of heterogeneity.
†Studies in Japanese population were excluded.
‡There is publication bias (Egger test, p=0.026).
DCAE, discontinuation due to adverse event; JAK, Janus kinase; SAE, serious adverse events.

treated patients was 1.18 (0.91 to 1.51 CI), and from 0.9 to 1.1 in biologic disease modifying antirheumatic drugs-treated patients.[28] Infections and malignancies were the most common causes of death in phase 3 and long-term extension studies in tofacitinib studies (see online supplementary table S6).

Seven AEs were meta-analysed to summarise the safety of the JAK PKi family (table 3), and no significant data were found. Meta-analysis to identify molecule-related AEs could be done just for tofacitinib (table 3). Thirteen AEs were meta-analysed. RR of hypercholesterolaemia was 1.70 (1.10 to 2.63 CI), without heterogeneity (I^2=0.0%, p=0.842), but with publication bias in funnel-plot (Egger test, p=0.05) (figure 1). RR for blood creatinine increase was 3.26 (0.84 to 12.60 CI) with heterogeneity (I^2=43.6%, p=0.170) and no publication bias in funnel-plot (Egger test, p=0.423). No source of heterogeneity was identified by metaregression.

Analysis of dose-related AE was done in RA tofacitinib-treated patients (see online supplementary tables S2 and S3).[37–41] IR of hypertension and elevation of blood creatinine phosphokinase was higher in the 10 mg twice daily (BID) dose group than in the 5 mg BID dose group. RR for nausea was 2.04 (0.77 to 5.40 CI) in the 5 mg BID group and 2.70 (1.05 to 6.90 CI) in the 10 mg BID group. RR for hypercholesterolaemia was 1.97 (1.14 to 3.40 CI) in the 5 mg BID group, and 2.84 (1.73 to 4.68 CI) in the 10 mg BID group.

Sensitivity analysis for tofacitinib AE including just full reports of RA trials with at least 12 weeks of exposure also found a significant RR for hypercholesterolaemia.

Safety of c-Kit inhibitors

IR of anaemia, diarrhoea, oedema, headache, nausea and rash were higher in imatinib-treated patients than the comparator groups. DCAE, diarrhoea, oedema, nausea, pruritus and rash were reported more common in patients treated with masitinib than their comparators (table 2).

Four AEs were meta-analysed to summarise the safety of the c-Kit PKi family (table 3). RR for oedema was 3.43 (CI 1.58 to 7.42) without heterogeneity (I^2 = 0%, p = 0.567) and no publication bias in funnel-plot (Egger test, p = 0.332) (figure 1), and 2.18 (CI 1.21 to 3.91) for DCAE with no heterogeneity (I^2=0%, p=0.790) and no publication bias (Egger test, p=0.085) (table 3). Meta-analysis to identify molecule-related AE could be done just for masitinib (table 3). RR for SAE in masitinib was 2.40 (CI 1.03 to 5.59) without heterogeneity (I^2=0.0%, p=0.547) and no publication bias (Egger test, p=0.293).

Safety of SyK inhibitors

Safety of Syk inhibition was only studied as fostamatinib molecule-related AE because there were no studies with other Syk inhibitors. IR for hypertransaminasemia, hypertension, diarrhoea and neutropenia were higher in fostamatinib-treated patients than in the comparator groups. SAE and rash were reported in fostamatinib-treated patients but not in the comparator groups (table 2). No cases of tuberculosis, neutropenic infection or fungal infection were reported in fostamatinib trials. Causes of death in fostamatinib-treated patients are available in online supplementary table S6.

Five AEs were meta-analysed to summarise the safety of fostamatinib (table 3). RR were 2.93 (CI 1.02 to 8.43) for hypertransaminasaemia, 2.80 (CI 1.58 to 5.99) for hypertension, 5.20 (CI 3.19 to 8.49) for diarrhoea, and 9.24 (CI 2.22 to 38.42) for neutropenia. All RR have no heterogeneity or publication bias (figure 1). Subanalysis of dose-related AE was not feasible due to the dose variability among studies. Frequencies of the AE stratified by dose are summarised in online supplementary table S4.

DISCUSSION

In this systematic review, we summarise the safety profile of PKi used for the treatment of RA. We have found a unique family and molecule-related AE, explained by target and off-target PKi inhibition.

The study has several limitations. First, this systematic review was focused on novel drugs still in development. Sometimes, data was only available in abstract form, and safety information did not allow for the estimation of the rate of AE. Second, the definition of AE varied across studies, and safety information was coded using MedDRA vocabulary terms that are not exclusive. Third, the need for pooling different treatment doses was a main obstacle to describe dose-dependent AE. Nevertheless, some dose-dependent AE in individual studies were reported. Finally, comparator arms were different, and this may have an impact on estimation of AE risks.

The present work was sensitive because strategy search included all synonyms and past names of all drugs. In addition, RCTs in disorders other than RA and healthy participants were included to identify drug-related AE regardless of underlying disease. Diseases with high comorbidity burdens, such as cancer and intense care pathologies, were excluded to avoid misinterpretation of events. Inclusion of a relatively heterogenous group of disorders in the meta-analysis is unlikely to be influenced by disease-specific considerations in view of the toxicities identified in the study. An additional strength is the level of evidence of the studies. All studies were CTs, and AE were actively pursued as determined by protocol. Our analysis did not assume a relationship between the drug and the AE. When frequency of AE was expressed as 'related to study drug', this was averted.

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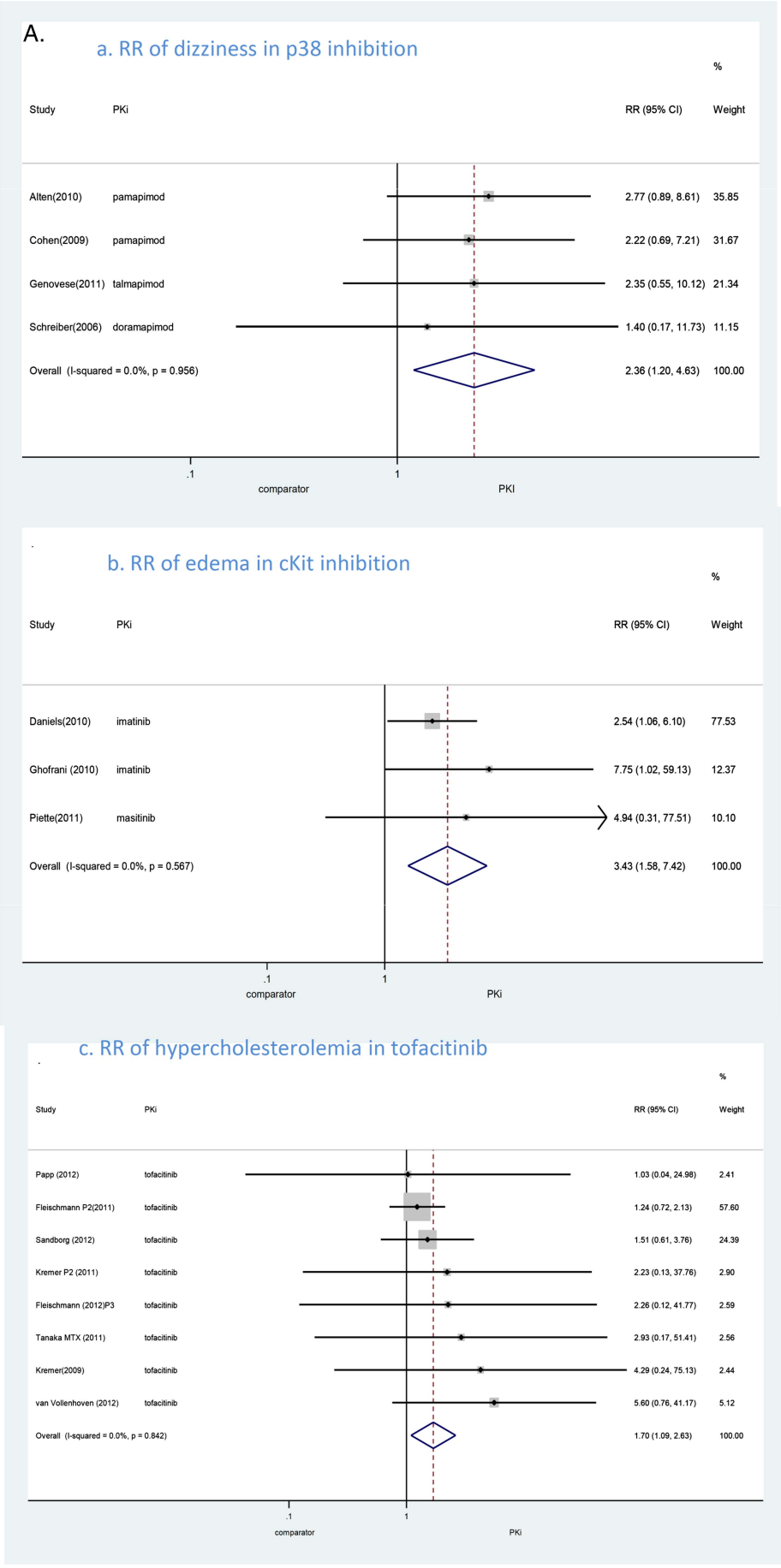

Figure 1 Relative risk (RR) of family and molecule-related adverse events. (A) a, RR of dizziness in p38 inhibition. b, RR of hypercholesterolaemia in tofacitinib. c, RR of oedema in cKit inhibition. (B) d, RR of hypertransaminasemia in fostamatinib. e, RR of hypertension in fostamatinib. f, RR of diarrhoea in fostamatinib. g, RR of neutropenia in fostamatinib.

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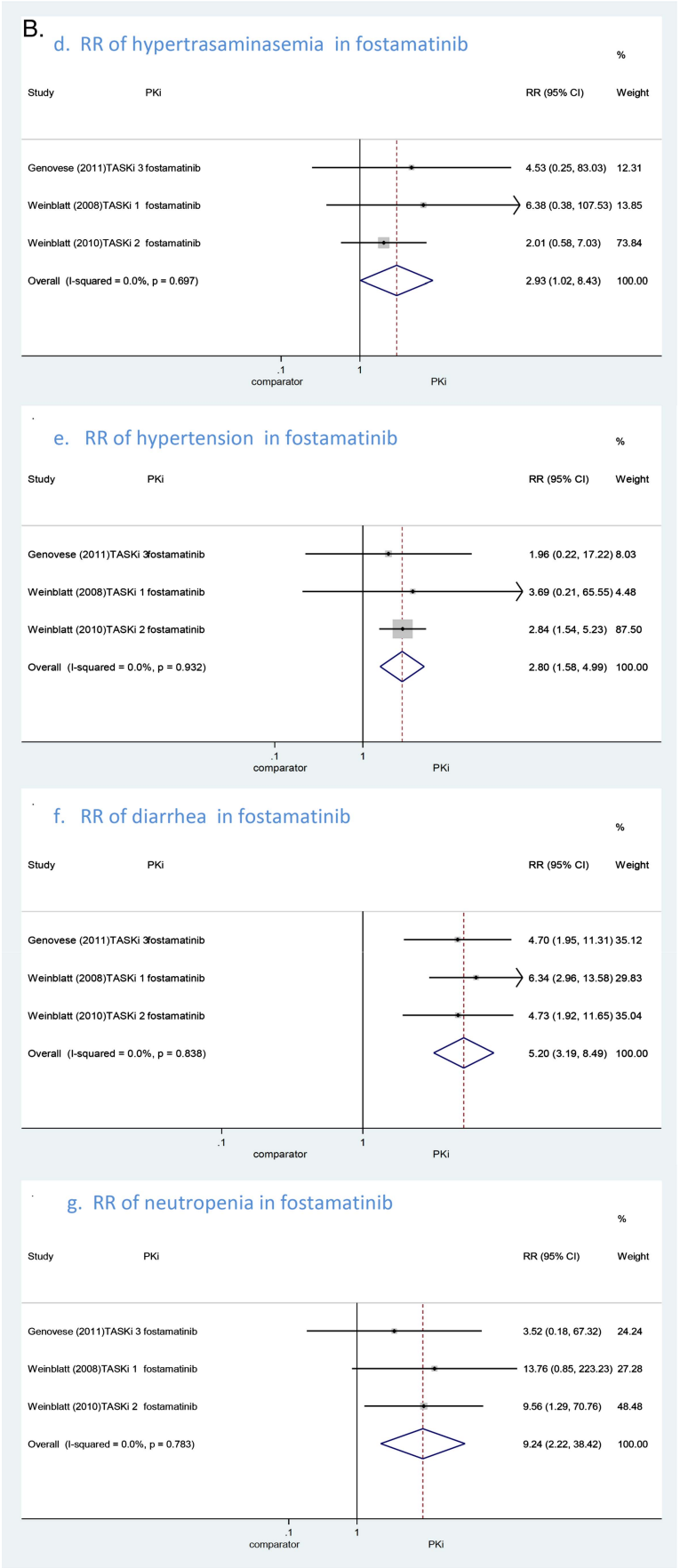

Figure 1 **(Continued)**

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Dizziness was more frequent in patients treated with pamapimod than in the comparator group. Dizziness may be family related AE of p38 inhibitors as evidenced by the significant RR in the meta-analysis of all patients treated with p38 inhibitors. Since p38 is present in the cerebellum, the inhibition of this kinase has already been proposed as explanation for this AE.[42] Rash was also more frequent in patients treated with talmapimod than in the comparator groups. This AE was not included in the meta-analyses of p38 inhibitors because there were not sufficient comparable measurements. However, skin toxicity has been described as reason for concluding the development of the p38 inhibitor SCIO-323.[24] The kinases MSK1 and MSK2 are p38 activated downstream kinases. In a model of toxic contact eczema, double deficiency in MSK1 and MSK2 leads to prolonged inflammation.[43]Thus, cutaneous toxicity could be a family related AE.

Hypercholesterolaemia was significantly higher in patients treated with tofacitinib than in the comparator group. Dose-dependent increase in mean serum total cholesterol, high-density lipoprotein, and low-density lipoprotein at week 6 occurs in CTs in patients with RA treated with tofacitinib.[44] Also, dose-related cholesterol increase was reported in patients with RA treated with the JAK3 inhibitor VX-509 in a phase 2 CT.[45] IL-6 signals primarily through JAK1 and JAK2, and hypercholesterolaemia, occur in patients treated with the anti-IL-6 receptor antibody tocilizumab.[46] It is conceivable that hypercholesterolaemia is caused by IL-6 signalling inhibition efficiently done by JAK inhibitors. Nevertheless, treatment of 24 patients with RA with the JAK1 inhibitor GLPG-0634 for 4 weeks and healthy volunteers for 10 days was not accompanied by hypercholesterolaemia.[47 48] It may be that exposure longer than 10 days is required before this abnormal laboratory finding happens. Blood creatinine increase was more frequent in patients treated with tofacitinib than in the comparator groups. In a phase 2a study in RA with baricitinib for 12 weeks, blood creatinine elevation was reported as well.[9] Unlike in the dose-ranging study of VX-509 for 12 weeks and in the limited study on GLPG-0634, there was no evidence of renal function impairment.[45] In the animal model of acute renal failure, activation of JAK2 by erythropoietin protects the kidney against the injury and dysfunction caused by ischemia-reperfusion.[49] JAK2 may have a role in preventing renal function impairment. Our data show that minor renal impairment might be related to the inhibition of JAK2. In agreement, selective inhibition of JAK1 with GLPG-0634 or JAK3 with VX-509 does not deteriorate kidney function.

Imatinib and masitinib share AE as oedema, rash, nausea, vomiting, diarrhoea and headache. These AEs were significantly more frequent in patients treated with imatinib than in the comparator arm (table 2). RR for oedema in the meta-analysis of patients treated with these two drugs was 3.43 (CI 1.58 to 7.42). Masitinib is the most specific cKit inhibitor, but also targets PDGFR. Imatinib inhibits several tyrosine kinase receptors including cKit and PDGFR. In animal models, imatinib promotes a vascular leakage syndrome through disruption of PDGF-regulated pericyte coverage of vessels.[50]Oedema may result from inhibition of PDGFR. Also, c-Kit immunopositive cells are considered to be pacemakers and/or mediators of neurotransmission in the gastrointestinal tract.[51] It could be speculated that nausea, vomiting and diarrhoea are related to inhibition of c-Kit and subsequent alteration of gastrointestinal function. Thus, oedema, nausea, vomiting and diarrhoea may be of c-Kit inhibitors family related AE.

Neutropenia and hypertransaminasemia were seen more frequently in patients treated with fostamatinib than in controls. The fostamatinib prodrug R406 may inhibit JAK1 and JAK3,[19] and JAKs mediate signalling in pathways triggered by haematopoietic growth factors. Consequently, neutropenia could be explained by inhibition of receptor activation of haematopoietic growth factors. Hypertension was also related to fosfamatinib in a dose-dependent manner (see online supplementary table S4). It could result from off-target inhibition of the vascular endothelial growth factor receptor 2 by fostamatinib that is more evident with higher doses.

Biologics and PKi are potent immune modulators with a significant efficacy in the treatment of RA. They share similar event rates of serious infections and malignancies. In addition, PKi have a unique safety profile related to target and off-target inhibition of selected PK, at times dose-related. Recognition of this information will lead to safer treatment of patients. Also, the development of kinome profiling techniques will help in the understanding of the mechanisms of action, and to the future design of new PKi with a better safety profile.

Acknowledgements We would like to acknowledge the invaluable assistance of Prof M Loza (USC) and Dr E Loza-Santamaría (Instituto de Salud Musculoesquelética) with the methodology.

Contributors ES: Literature search and selection papers for systematic review; interpretation of data and drafting the article. JRM: Selection papers for inclusion. LC: Study design, interpretation of data, drafting the article, selection papers for inclusion and revising it critically for important intellectual content. JJGR: Conception and study design, interpretation of data, drafting the article and revising it critically for important intellectual content. All authors gave final approval of the version to be published.

Funding This study was partially supported by grants (Spain), and RETICS Program, RD08/0075 (RIER) of the Instituto de Salud Carlos III (Spain)

Competing interests JJ G-R is on the advisory boards of Schering-Plough, Wyeth, MSD, Bristol Meyers Squibb and Roche, and has received lecture fees from Abbott Laboratories, Wyeth, MSD, Roche, Bristol Meyers Squibb and Schering-Plough. LC has received lectures fees from Abbott Laboratories and Pfizer. ES: None declared. JRM: None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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Safety profile of protein kinase inhibitors in rheumatoid arthritis: systematic review and meta-analysis

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Ann Rheum Dis 2014 73: 871-882 originally published online April 18, 2013
doi: 10.1136/annrheumdis-2012-203116

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