RISK OF SERIOUS INFECTIONS IN PATIENTS WITH PSORIASIS ON BIOLOGIC THERAPIES

A Systematic Review and Meta-Analysis

Zenas Z N Yiu (NIHR Doctoral Research Fellow)^{1,2,3,} Lesley S Exton³, Zarif Jabbar-Lopez³, M Firouz Mohd Mustapa³, Eleanor J Samarasekera³, A David Burden³, Ruth Murphy³ Caroline M Owen³, Richard Parslew³, Vanessa Venning³, Darren M Ashcroft², Christopher E M Griffiths¹, Catherine H Smith³, Richard B Warren^{1,3} ¹Centre for Dermatology and ²Centre for Pharmacoepidemiology and Drug Safety. The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

³British Association of Dermatologists Biologics Guideline Development Group

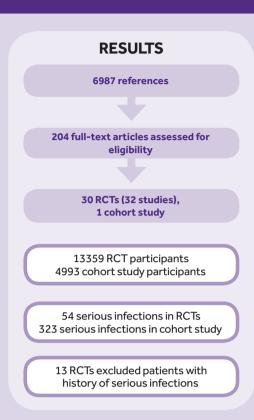
WHY IS THIS STUDY NEEDED?

- 1. Evidence gap for patients with psoriasis; current evidence extrapolated from rheumatoid arthritis
- 2. New biologic therapies approved for psoriasis since last systematic review ustekinumab, secukinumab
- 3. Inform guideline development and decision making

METHODS

- Population patients with primarily psoriasis
- Intervention adalimumab, etanercept, infliximab, ustekinumab, secukinumab
- Comparator any above biologic, placebo, other systemics
- Outcome serious infection (SI; investigator defined)

- Study design systematic reviews; randomised controlled trials (RCTs); prospective cohort studies
- Key exclusions n < 50; indirect populations (e.g. patients with rheumatoid arthritis)
- Search conducted in PubMed, Medline, Embase, Cochrane, inception to 29/09/2015
- ▶ Two assessors screened title/abstracts
- National Clinical Guideline Centre (NCGC) data extraction tool
- National Institute for Health and Care Excellence (NICE) risk of bias checklists
- Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for quality of evidence
- Meta-analysis pooled Peto's odds ratio (OR); l² test for heterogeneity



RISK OF BIAS AND QUALITY OF EVIDENCE

- 26 (83.9%) low risk of selection bias; 26 (83.9%) low risk of performance bias; 27 (87.1%) no clear reporting of investigator blinding (information bias), 1 openlabel RCT, 29 (93.5%) low risk of attrition bias; no clear publication bias from funnel plot
- 2. Overall quality (GRADE) low very low due to very serious imprecision / serious risk of bias
- 3. 3 out of 33 studies reported their definition of SI outcome

Forest plot for dose-independent comparison between biologic therapies and placebo at week 12-16, adults, RCT

NO DIFFERENCE IN RISK OF SI

GRADE quality

Low – etanercept, secukinumab

Very low – /, adalimumab, ustekinumab

	Biologic		Placebo		Peto Odds Ratio		Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl	
1.1.1 Etanercept								
Van de Kerkhof BJD 2008	0	96	0	46		Not estimable		
Strober BJD 2011	0	139	0	72		Not estimable		
Gottlieb BJD 2011	1	141	0	68	2.7%	4.40 [0.07, 288.78]		
Papp BJD 2005	0	390	1	193	2.7%	0.05 [0.00, 3.14]	·	
Tyring Lancet 2006	0	311	1	307	3.1%	0.13 [0.00, 6.73]	· · · · · · · · · · · · · · · · · · ·	
Bachelez Lancet 2015	2	336	0	108	4.5%	3.76 [0.15, 95.42]		
Griffiths Lancet 2015 UNCOVER-3	0	382	2	193	5.5%	0.05 [0.00, 0.95]	· · · · · · · · · · · · · · · · · · ·	
Griffiths Lancet 2015 UNCOVER-2	3	358	0	168	8.0%	4.37 [0.38, 49.73]		
Subtotal (95% CI)		2153		1155	26.5%	0.71 [0.19, 2.71]		
Total events	6		4					
1.1.2 Infliximab Yang CMJ 2012	0	84 84	0	45 45		Not estimable Not estimable		
Subtotal (95% CI)		84		45		Not estimable		
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable	1							
1.1.3 Adalimumab								
Gordon NEJM 2015	0	43	0	42		Not estimable		
Saurat BJD 2008	0	108	0	53		Not estimable		
Asahina JD 2010	1	123	0	46	2.4%	3.95 [0.05, 322.96]		
Gordon JAAD 2006	1	96	0	52	2.8%	4.67 [0.08, 283.50]		
Menter JAAD 2008	5	814	4	398	24.3%	0.59 [0.15, 2.38]		
Subtotal (95% CI)		1184		591	29.5%	0.84 [0.24, 2.97]		
Total events	7		4					
Heterogeneity: Chi ² = 1.40, df = 2 (P	= 0.50); l²	= 0%						
Test for overall effect: Z = 0.27 (P = 0	J.79)							

Forest plot for dose-independent comparison between biologic therapies and acitretin/phototherapy, adults, cohort study

ADALIMUMAB 2.5x RISK OF SI

GRADE quality

Low – adalimumab

Very low - infliximab, adalimumab, ustekinumab

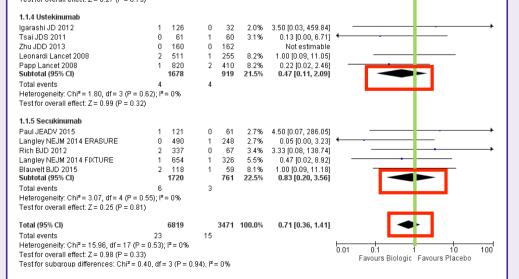
Study or Subgroup log[Ha;	zard Ratio]	SE	Total	oids/Phototherapy Total	Moight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% Cl
7.1.1 Etanercept vs Retinoid/Pho		30	Total	Total	weight	IV, FIXED, 95% CI	IV, FIXed, 95% CI
Kalb JAMA Derm 2015	0.2546	0.4349	461	1610	100.0%	1.29 (0.55, 3.03)	
Subtotal (95% CI)	0.2010	0.1010	461	1610		1.29 [0.55, 3.03]	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.59 (P	= 0.56)						
7.1.2 Infliximab vs Retinoid/Phote	otherapy						
Kalb JAMA Derm 2015	0.5766	0.5219	246		100.0%	1.78 [0.64, 4.95]	
Subtotal (95% CI)			246	1610	100.0%	1.78 [0.64, 4.95]	
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.10 (P	= 0.27)						
7.1.3 Adalimumab vs Retinoid/Ph	nototherapy						
Kalb JAMA Derm 2015	0.9243	0.275	1157			2.52 [1.47, 4.32]	
Subtotal (95% CI)			1157	1610	100.0%	2.52 [1.47, 4.32]	-
Heterogeneity: Not applicable	0.0000						
Test for overall effect: Z = 3.36 (P	= 0.0008)						
7.1.4 Ustekinumab vs Retinoid/P	hototherapy	/					_
Kalb JAMA Derm 2015	0.2311	0.3299	1519		100.0%	1.26 [0.66, 2.41]	
Subtotal (95% CI)			1519	1610	100.0%	1.26 [0.66, 2.41]	
Heterogeneity: Not applicable	0.400						
Test for overall effect: Z = 0.70 (P	= 0.48)						
							0.1 0.2 0.5 1 2 5 10 Favours Biologic Favours Comparator

KEY LIMITATIONS

- 1. Lack of long-term data for RCTs
- 2. Study population for the RCTs different

<u>SUMMARY</u>

1. No increased short-term risk



- from target population in real-world settings
- 3. Definitions of adverse events outcome (SI) not clearly reported

ACKNOWLEDGEMENTS

ZZNY is funded by a National Institute for Health Research (NIHR) Doctoral Research Fellowship (Ref no: DRF-2015-08-089). This is a summary of independent research funded by the National Institute for Health Research (NIHR) Doctoral Research Fellowship. The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health. CEMG is an NIHR Senior Investigator and CEMG, CHS, DMA, ADB and RBW are funded in part by the Medical Research Council (MR/ L011808/1).

The authors would like to acknowledge the funding made available by the British Association of Dermatologists for the consultancy work provided by the National Clinical Guideline Centre. of serious infection from RCT data for any biologic used in patients with psoriasis

2. Adalimumab 2.5x risk of SIs as compared to acitretin/ phototherapy cohort

3. Further well designed observational studies needed to clarify risk of SI in patients with psoriasis on biologic therapies



1824 The University of Manchester



Manchester Academic Health Science Centre

