

Electronic Supplementary Material 2

Article Title: Methods to compare Adverse Events in Twitter to FAERS, Drug Information Databases, and Systematic Reviews: Proof of Concept with Adalimumab

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Appendix 2: Systematic Reviews of Adalimumab and Reported Adverse Drug Events

| Systematic Review | Type of Evidence | Adverse Effect in Humira Patients | Adverse Effect in Control Group Patients (Placebo) |
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| Results Presented as Rates (Highest First) | | | |
| Archer 2016 | 4 RCTs | Infections 32/223 (14.3%), 116/257 (45.1%), 17/90 (18.9%) Injection site reactions 13/223 (5.8%), 31/257 (12.1%), 10.5 events per 100 PYs, 7/90 (7.8%) Serious infections 0/223 (0%), 4/257 (1.6%), 3.4 events per 100 PYs, 3/90 (3.3%) Haematological reactions 5/257 (1.9%), 1/90 (1.1%) Hepatobiliary events 0.5 events per 100 PYs, 1/90 (1.1%) Tuberculosis <0.1 events per 100 PYs, 1.0 events per 100 PYs Malignancies 0/223 (0%), 2/257 (0.8%), 1.0 events (excluding lymphoma) per 100 PYs, 1 events per 100 PYs for lymphoma, 1/90, (1.1%) | Infections 35/223 (15.7%), 103/260 (39.1%), 15/96 (15.6%) Injection site reactions 7/223 (3.1%), 10/260 (3.8%), 2/96 (2.1%) Serious infections 3/223 |

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| | | Heart failure 1/257 (0.4%), 0.2 events per 100 PYs Lupus-like syndrome 1/257 (0.4%) | (1.3%) (one pneumonia, one sepsis, one staphylococcal wound infection), 5/260 (1.9%), 0/96 (0%) Malignancies 2/223 (0.9%), 0/257 (0%), 0/96 (0%) Hepatobiliary events 1//96 (1.0%) haematological reactions 0/257 (0%), 1//96 (1.0%) Lupus-like syndrome, Heart failure, Tuberculosis 0 |
| Dziechciarz 2016 | 1 RCT and 10 case series | Infections 162/599 Injection sites reactions 89/599 Haematological (serious) 24/599 Allergic reactions (serious) 10/599 Hepatic-related (serious) 10/599 Arthralgia/myalgia 7/599 Xerosis 6/599 Abdominal pain 5/599 Headache 5/599 Nausea 5/599 Allergy 4/599 Abdominal abscess (serious) 3/599 Depigmentation acne 3/599 Fever 3/599 Rash 3/599 Deaths from central catheter sepsis 2/599 C. Difficile infection (serious) 2/599 Perianal abscess (serious) 2/599 Psoriasis 2/599 Tiredness 2/599 Tympanic perforation 1/599 Dizziness 1/599 Hair loss 1/599 Dyspnoea 1/599 Transient visual loss 1/599 Stomal bleeding 1/599 Itching 1/599 Numbness 1/599 Medulloblastoma (serious) 1/599 Meningitis (serious) 1/599 | |

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| | | Anal abscess (serious) 1/599 Stomal abscess with fistula (serious) 1/599 Colonic obstruction and abscess (serious) 1/599 Seton placement (serious) 1/599 Staphylococcal folliculitis (serious) 1/599 Scarlet fever (serious) 1/599 Disseminated histoplasmosis(serious) 1/599 Gastroenteritis (serious) 1/599 H1N1 influenza (serious) 1/599 Viral infection (serious) 1/599 Yersinia infection (serious) 1/599 | |
| Wang 2014 | 4 RCTs (not all report all AEs) | Infection 119/528 RR 1.22 (0.98-1.60) Injection-site reaction 48/437 RR 4.88 (1.97-12.09) P=0.0006 | Infection 63/316 Injection-site reaction 5/222 |
| Dretzke 2011 | 4 RCTs (all included in Huang 2011) | All infusion reactions 164/938 (17.48%) Serious infection 16/938 (1.71%) TB 2/938 (0.21%) Cancer 0/938 (0%) Death 0/938 (0%) Lupus-like syndrome 0/421 Demyelinating disorders 0/554 | All infusion reactions 40/519 (7.71%) Serious infection 13/519 (2.50%) Cancer 2/519 (0.39%) Death 0/519 (0%) TB 0/519 (0%) Lupus-like syndrome 0/258 Demyelinating disorders 0/279 |
| Huang 2011 | 4 RCTs (all included in Dretzke 2011) | 2 Induction trials Infection site reaction 86/384 P=0.05 Infection 63/384 P=0.21 2 Maintenance trials Infection 254/554 P=0.64 Infection site reaction 81/554 P=0.85 Reported other AEs such as arthralgia, nasopharyngitis, headache, nausea, fatigue, abdominal pain, pharyngolaryngeal pain | 2 Induction trials Infection 51/240 Infection site reaction 30/240 2 Maintenance trials Infection 114/279 Infection site reaction 11/279 |
| Rodgers 2011 | 2 RCTS (1 RCT overlap with Wiens 2010 but different outcomes extracted) and 10 uncontrolled studies | ADA RCT (n=102) Infections 17.6% Upper respiratory tract infection (URTI) 13.7% RCT (n=315) Upper respiratory tract infection (URTI) 12.6% Nasopharyngitis 9.9% Serious infection 1 Death 0 | Placebo RCT (n=102) Infections 32.7% Upper respiratory tract infection (URTI) 8.2% Serious infection 1 RCT (n=315) |

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| | | 10 Non-RCTs Infections 9.12%/15.20%/45.30% Serious infections 2.20%/3.10%/5.10%/7.30%/1.20%/2.70%/6.60%/0.40%/6.30% Cancers 1.10%/0.70%/0.20%/0.10% Mortality 0.90%/0.50%/0.20% TB 0.18%/0.30%/0%/0.08%/0.40%/0.30%/0.20%/0.30% | Upper respiratory tract infection (URTI) 14.8% Nasopharyngitis 9.4% Death 0 |
| Díaz-Lagares 2010 | 17 case reports/case series and 1 prospective cohort study | Local skin reaction 3/54 Angioedema 1/54 Lung fibrosis 1/54 | |
| Da 2012 | 1 RCT and 9 open-label cohort studies | Fungal pneumonia 6% (1/16) Dehydration 1% (1 or 2/159) Pruritic erythema 2% (1/50) Injection site pain, headache, fever, Psoriasiform dermatitis, viral upper respiratory tract infection, headache, Abdominal pain, arthralgia, headache, injection-site irritation, fatigue, Crohn's disease exacerbation, Dermatological problems, injection-site discomfort, Injection-site reaction, Upper respiratory tract infection, headache, bronchitis, rash, fatigue, arthritic pain, abdominal pain, back pain, nausea, perianal abscess, numbness, injection-site reaction, Dermatological problems, nausea/vomiting, diarrhea, dizziness, muscle/limb pain, arthralgia, cough, dysphagia, fatigue, weakness, metrorrhagia, fever, Injection-site reaction, headache, upper respiratory tract infection, dermatitis, pharyngitis, otitis, abdominal pain, fever, palpitations, tooth abscess, Injection-site reaction, facial rash, pruritus, dizziness, sinusitis, rhinitis SAES - Abdominal abscess, tuberculous meningitis, Crohn's disease exacerbation, intestinal obstruction, abdominal pain, gastroenteritis, abscess, ileal stenosis, constipation, pneumonia, dehydration, nephrolithiasis, bronchospasm, dehydration, fungal pneumonia, Abdominal pain, seizure, Pruritic erythema | |
| McLeod 2007 | 2 RCTs | Infectious AEs 60 patients (24%) and 84 patients (34%) Injection site reactions 24 patients and 25 patients (10%) Hypersensitivity 1 patient Death, cancer, demyelinating disease 0 | Infectious AEs 26 patients (17%) and 32 patients (26%) Injection site reactions 7 patients 5% Hypersensitivity, Death, cancer, demyelinating disease 0 |
| Results Presented as Risk Ratios Only (Highest First) | | | |
| Wiens 2010 | 6 RCTs (1 RCT overlap) | ADA Deaths N=2428 RR 2.52 (0.72–8.86) p=0.15 | |

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| | with Rodgers 2011 but different outcomes extracted) | Serious infections N=2300 RR 2.22 (0.83–5.99) p=0.11 Malignancy N=1467 RR 0.55 (0.14–2.11) p=0.38 | |
| Results Presented as Events/Patient-years (Highest First) | | | |
| Shepherd 2016 | 1 RCT | n=38 18.3 patient-years Related to injection-site reaction 73 (4.0) Contusion 12 (0.7) Excoriation 10 (0.6) Viral infection 7 (0.4) Upper respiratory tract infection 6 (0.3) Nasopharyngitis 5 (0.3) Vomiting 4 (0.2) Gastroduodenitis 0 | n=37 15 patient-years Related to injection-site reaction 57 (3.8) Contusion 7 (0.5) Nasopharyngitis 6 (0.4) Upper respiratory tract infection 5 (0.3) Viral infection 3 (0.2) Vomiting 2 (0.1) Excoriation 1 (0.1) Gastroduodenitis 1 (0.1) |
| Burmester 2013 | 71 clinical trials including RCTs, open-label trials and long-term extension studies (not listed) | Events/100 patient-years Serious infections Rheumatoid arthritis 4.6, Juvenile idiopathic arthritis 2.0, Ankylosing spondylitis 1.4, Psoriatic arthritis 2.8, Psoriasis 1.7, Crohn’s disease 6.7 Malignancies excluding lymphoma and NMSC Rheumatoid arthritis 0.9, Juvenile idiopathic arthritis 0, Ankylosing spondylitis 0.2, Psoriatic arthritis 0.2, Psoriasis <0.1, Crohn’s disease <0.1 Any AE leading to death Rheumatoid arthritis 0.8, Juvenile idiopathic arthritis 0, Ankylosing spondylitis <0.1, Psoriatic arthritis 0.3, Psoriasis 0.2, Crohn’s disease 0.1 Active tuberculosis Rheumatoid arthritis 0.3, Juvenile idiopathic arthritis 0, Ankylosing spondylitis 0, Psoriatic arthritis 0.2, Psoriasis 0.1, Crohn’s disease <0.1 NMSC† Rheumatoid arthritis 0.2, Juvenile idiopathic arthritis 0, Ankylosing spondylitis 0.3, Psoriatic arthritis 0.1, Psoriasis 0.1, Crohn’s disease 0.1 CHF Rheumatoid arthritis 0.2, Juvenile idiopathic arthritis 0, Ankylosing spondylitis 0.1, Psoriatic arthritis 0, Psoriasis <0.1, Crohn’s disease 0 New onset/worsening of psoriasis Rheumatoid arthritis <0.1, Juvenile idiopathic arthritis 0, Ankylosing spondylitis <0.1, Psoriatic arthritis 0.1, Psoriasis <0.1, Crohn’s disease <0.1 Opportunistic infections Rheumatoid arthritis <0.1, Juvenile idiopathic arthritis 0, Ankylosing spondylitis 0, Psoriatic arthritis 0, Psoriasis 0, Crohn’s disease <0.1 | |

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| | | <p>Demyelinating disorder Rheumatoid arthritis <0.1, Juvenile idiopathic arthritis 0, Ankylosing spondylitis <0.1, Psoriatic arthritis 0, Psoriasis 0, Crohn's disease 0.1</p> <p>Lupus-like syndrome Rheumatoid arthritis <0.1, Juvenile idiopathic arthritis 0, Ankylosing spondylitis 0.1, Psoriatic arthritis 0, Psoriasis 0, Crohn's disease <0.1</p> <p>Lymphoma Rheumatoid arthritis 0.1, Juvenile idiopathic arthritis 0, Ankylosing spondylitis <0.1, Psoriatic arthritis 0.2, Psoriasis <0.1, Crohn's disease <0.1</p> <p>Melanoma Rheumatoid arthritis <0.1, Juvenile idiopathic arthritis 0, Ankylosing spondylitis <0.1, Psoriatic arthritis 0, Psoriasis 0.2, Crohn's disease 0</p> <p>Standardized Incidence Rates</p> <p>Lymphomas Rheumatoid arthritis 2.74 (1.83-3.93), Ankylosing spondylitis 1.93 (0.03-10.7), Psoriatic arthritis 5.88 (0.66-21.2) Psoriasis 0.63 (0.01-3.49), Crohn's disease 2.58 (0.29-9.31)</p> <p>All malignancies Rheumatoid arthritis 0.93 (0.82-1.06), Ankylosing spondylitis 0.51 (0.16-1.19), Psoriatic arthritis 0.68 (0.22-1.59), Psoriasis 0.96 (0.65-1.36), Crohn's disease 1.52 (0.95-2.31)</p> <p>NMSC Rheumatoid arthritis 1.39 (1.19-1.60), Ankylosing spondylitis (0.80 (0.29-1.74), Psoriatic arthritis 1.25 (0.46-2.72), Psoriasis 1.76 (1.26-2.39), Crohn's disease 2.29 (1.44-3.47)</p> <p>Standardized Mortality Rates</p> <p>All indications 0.66 (0.53-0.80), Rheumatoid arthritis 0.69 (0.56-0.85), Ankylosing spondylitis, Psoriatic arthritis 0.43 (0.01-2.39), Psoriasis 0.2 (0-1.11), Crohn's disease 0.57 (0.12-1.68)</p> | |
| Asking 2011 | 23 RCTs (not listed) | <p>All cancers including non-melanoma skin cancer Events/person-years 41/2859, Rate/100,000 1434, Hazards ratio (1.40 (0.78-2.61)</p> <p>Non-melanoma skin cancer only Events/person-years 23/2863, Rate/100,000 803, Hazards ratio 2.59 (1.01, 7.67)</p> <p>All site cancers excluding non-melanoma skin cancer Events/person-years 18/2869, Rate/100,000 627, Hazards ratio 0.92 (0.42, 2.14)–1.09 (0.56, 2.23)</p> | <p>All cancers including non-melanoma skin cancer Events/person-years 15/1465, Rate/100,000 1024</p> <p>All site cancers excluding non-melanoma skin cancer Events/person-years 10/1468, Rate/100,000 681</p> <p>Non-melanoma skin cancer only</p> |

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| | | | Events/person-years 5/1468, Rate/100,000 341 |
| Leonardi 2011 | 13 Clinical Trials (not listed) | <p>AEs for >5% of patients were nasopharyngitis, upper respiratory infection, and headache</p> <p>Placebo-controlled phase</p> <p>Infectious AE 572 events, 154.4 events/100 PYs</p> <p>Serious infectious AE 9 events, 2.43 events/100 PYs</p> <p>Allergic reaction 7 events, 1.89 events/100 PYs</p> <p>NMSC 5 events, 1.35 events/100 PYs</p> <p>Malignancies (excluding NMSC) 3 events, 0.81 events/100 PYs</p> <p>Fatal AE 0 events, 0 events/100 PYs</p> <p>Opportunistic infections (excluding TB) 1 events, 0.27 events/100 PYs</p> <p>TB 0 events, 0 events/100 PYs</p> <p>Congestive heart failure 1 events, 0.27 events/100 PYs</p> <p>Lymphoma 0 events, 0 events/100 PYs</p> <p>Demyelinating disease 0 events, 0 events/100 PYs</p> <p>Lupus-like syndrome 0 events, 0 events/100 PYs</p> <p>AES in All Adalimumab treatment population</p> <p>Infectious AE 4301 events, 88.8 events/100 PYs</p> <p>Serious infectious AE 80 events, 1.65 events/100 PYs</p> <p>Allergic reaction 51 events, 1.05 events/100 PYs</p> <p>Malignancies (excluding NMSC) 35 events, 0.72 events/100 PYs</p> <p>NMSC 34 events, 0.70 events/100 PYs</p> <p>Opportunistic infections (excluding TB) 20 events, 0.41 events/100 PYs</p> <p>Congestive heart failure 11 events, 0.23 events/100 PYs</p> <p>Fatal AE 9 events, 0.19 events/100 PYs</p> <p>TB 7 events, 0.14 events/100 PYs</p> <p>Lupus-like syndrome 3 events, 0.06 events/100 PYs</p> <p>Lymphoma 1 events, 0.02 events/100 PYs</p> <p>Demyelinating disease 1 events, 0.02 events/100 PYs</p> <p>Every other week population</p> <p>Infectious AE 2133 events, 74.7 events/100 PYs</p> <p>Serious infectious AE 39 events, 1.37 events/100 PYs</p> <p>NMSC 21 events, 0.74 events/100 PYs</p> <p>Malignancies (excluding NMSC) 17 events, 0.60 events/100 PYs</p> <p>Allergic reaction 15 events, 0.53 events/100 PYs</p> <p>Opportunistic infections (excluding TB) 7 events, 0.25 events/100 PYs</p> <p>Congestive heart failure 6 events, 0.21 events/100 PYs</p> <p>TB 5 events, 0.18 events/100 PYs</p> <p>Fatal AE 4 events, 0.14 events/100 PYs</p> <p>Demyelinating disease 1 events, 0.04 events/100 PYs</p> <p>Lupus-like syndrome 0 events, 0 events/100 PYs</p> | <p>Infectious AE 200 events, 115.6</p> <p>Serious infectious AE 5 events, 2.89 events/100 PYs</p> <p>NMSC 5 events, 1.35 events/100 PYs</p> <p>Malignancies (excluding NMSC) 2 events, 1.16 events/100 PYs</p> <p>Allergic reaction 1 events, 0.58 events/100 PYs</p> <p>Lymphoma 0 events, 0 events/100 PYs</p> <p>Fatal AE 0 events, 0 events/100 PYs</p> <p>Opportunistic infections (excluding TB) 0 events, 0 events/100 PYs</p> <p>TB 0 events, 0 events/100 PYs</p> <p>Congestive heart failure 0 events, 0 events/100 PYs</p> <p>Demyelinating disease 0 events, 0 events/100 PYs</p> <p>Lupus-like syndrome 0 events, 0 events/100 PYs</p> |

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| | | Lymphoma 0 events, 0 events/100 PYs | |
| Malottki 2011 | 3 uncontrolled studies | Serious infection rate 10/100 patient-years TB 0.4/100 patient-years and another study TB 1 Cellulitis 1 Herpes zoster 1 Hypersensitivity reaction 1 Anaphylactic response 0 Also Injection site reaction/infusion reaction | |
| Burmester 2009 | 36 clinical trials including RCTs, open-label trials and long-term extension studies (not listed) | Events/100 patient-years Serious infections Rheumatoid arthritis 4.65 Psoriatic arthritis 2.81 Ankylosing spondylitis 1.11 Juvenile idiopathic arthritis 2.76 Psoriasis 1.32 Crohn's disease 5.18 Tuberculosis Rheumatoid arthritis 0.29 Psoriatic arthritis 0.30 Ankylosing spondylitis 0 Juvenile idiopathic arthritis 0 Psoriasis 0.12 Crohn's disease 0.13 Opportunistic infections Rheumatoid arthritis 0.09 (17 cases) Psoriatic arthritis 0 Ankylosing spondylitis 0 Juvenile idiopathic arthritis 0 Psoriasis 0 Crohn's disease 0.08 (2 cases) Histoplasmosis Rheumatoid arthritis 0.03 Psoriatic arthritis 0 Ankylosing spondylitis 0 Juvenile idiopathic arthritis 0 Psoriasis 0 Crohn's disease 0 Malignancies excluding lymphoma and NMSC Rheumatoid arthritis 0.76 Psoriatic arthritis 0.30 Ankylosing spondylitis 0.08 Juvenile idiopathic arthritis 0 Psoriasis 0.49 0.46 Lymphoma Rheumatoid arthritis 0.12 Psoriatic arthritis 0.20 Ankylosing spondylitis 0.08 Juvenile idiopathic arthritis 0 Psoriasis 0 Crohn's disease 0.08 NMSC Rheumatoid arthritis 0.17 Psoriatic arthritis 0 Ankylosing spondylitis 0.08 Juvenile idiopathic arthritis 0 Psoriasis 0.12 0 Demyelinating disorder Rheumatoid arthritis 0.05 Psoriatic arthritis 0 Ankylosing spondylitis 0.08 Juvenile idiopathic arthritis 0 Psoriasis 0 Crohn's disease 0.13 Lupus-like syndrome Rheumatoid arthritis 0.07 Psoriatic arthritis 0 Ankylosing spondylitis 0 Juvenile idiopathic arthritis 0 Psoriasis 0 Crohn's disease 0.04 Congestive heart failure Rheumatoid arthritis 0.23 Psoriatic arthritis 0 Ankylosing spondylitis 0.16 Juvenile idiopathic arthritis 0 Psoriasis 0 Crohn's disease 0 Also lymphomas, demyelinating disease, lupus-like syndrome, oral candidiasis, histoplasmosis, cytomegaloviral infections, coccidioidomycosis, toxoplasmosis, listeriosis, nocardiosis, aspergilloma, Pneumocystis, jiroveci infection, oesophageal candidiasis, candida sepsis, Mortality | |
| List Adverse Effects with incomplete or No Numerical Data | | | |
| Ma 2009 | RCTs and open-label cohorts | SAEs: Perioral cellulitis, central demyelination, toxic retinopathy, colorectal adenocarcinoma, psoriasis, ileal perforation, Death (2) Psoriasis, angioneurotic oedema, liver abscess, dental abscess, Acute nasopharyngitis, bowel obstruction, Dehydration, Fungal pneumonia, Pruritic erythema, New onset seizure, worsening abdominal pain, | |

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| | | Pruritis, Death (2), tumours (7), suicidal attempt (1), severe infection (7), Interstitial keratitis |
| Chen 2006 | RCTs, data from postmarketing surveillance, major observational studies and various registries including the BSRBR | Serious infection, malignancy (4), death (4 vs 1 placebo) |
| Song 2014 | 6 RCTs | AEs: infections, injection site reactions, abdominal tenderness, nausea, flatulence, nasopharyngitis, pharyngitis, and headache SAEs: pneumonia, septicemia, tuberculosis, drug-induced lupus, and tumor. |
| Navarro-Sarabia 2005/2006 | RCTs or CCTs | Injection site reactions, headaches, allergy-like symptoms, colds, upper respiratory tract, infections, rhinitis |