Table S1: MedRA codes for diagnoses possibly related to perforations

pt_code	pt_term
10000099	Abdominal wall abscess
10000285	Abscess intestinal
10000582	Acquired tracheo-oesophageal fistula
10002156	Anal fistula
10002157	Anal fistula excision
10002248	Anastomotic ulcer perforation
10002924	Aorto-duodenal fistula
10003012	Appendicitis perforated
10009995	Colonic fistula
10013536	Diverticular fistula
10013538	Diverticulitis
10013541	Diverticulitis intestinal haemorrhagic
10013828	Duodenal fistula
10013832	Duodenal perforation
10013849	Duodenal ulcer perforation
10013850	Duodenal ulcer perforation, obstructive
10017815	Gastric perforation
10017835	Gastric ulcer perforation
10017836	Gastric ulcer perforation, obstructive
10017866	Gastritis haemorrhagic
10017877	Gastrointestinal fistula
10017954	Gastrointestinal gangrene
10017955	Gastrointestinal haemorrhage
10018001	Gastrointestinal perforation
10021305	Ileal perforation
10021310	Ileal ulcer perforation
10022647	Intestinal fistula
10022694	Intestinal perforation
10023174	Jejunal perforation
10023178	Jejunal ulcer perforation
10023804	Large intestine perforation
10030181	Oesophageal perforation
10034354	Peptic ulcer perforation
10034358	Peptic ulcer perforation, obstructive
10034397	Perforated peptic ulcer oversewing
10034649	Peritoneal abscess
10034674	Peritonitis
10038073	Rectal perforation
10038975	Retroperitoneal abscess
10041103	Small intestinal perforation
10046274	Upper gastrointestinal haemorrhage
10048946	Anal abscess
10048947	Rectal abscess
10049583	Douglas' abscess
10049764	Appendiceal abscess
10050362	Anovulvar fistula
10050953	Lower gastrointestinal haemorrhage
10051425	Enterocutaneous fistula

10052211	Oesophageal rupture
10052457	Perineal abscess
10052488	Oesophageal ulcer perforation
10052814	Perirectal abscess
10052931	Colon fistula repair
10052991	Intestinal fistula repair
10053267	Rectal fistula repair
10056086	Paraoesophageal abscess
10056346	Anastomotic haemorrhage
10056991	Enterocolonic fistula
10056992	Oesophagobronchial fistula
10058381	Oesophageal fistula repair
10059175	Intestinal haemorrhage
10060921	Abdominal abscess
10061248	Intestinal ulcer perforation
10061249	Intra-abdominal haemorrhage
10061820	Diverticular perforation
10061975	Gastrointestinal ulcer perforation
10062065	Perforated ulcer
10062070	Peritonitis bacterial
10062570	Enterovesical fistula
10065713	Gastric fistula
10065879	Gastrointestinal anastomotic leak
10066870	Aorto-oesophageal fistula
10066892	Rectourethral fistula
10067091	Gastropleural fistula
10068792	Gastrosplenic fistula
10073573	Colonic abscess

Table S2: Demographics, comedication and clinical presentation of patients with LIP under TCZ

Case No.	Event	Date of LIP event	TCZ treatment course	CRP values	Days between death and LIP and cause of death (COD)	Age at LIP	Clinical presentation
1	a) Admission to hospital due to suspected vesico-sigmoidal fistula - elective surgery beginning of december 2010 b) during hospital stay: diverticulum perforation of colon transversum	11/2010 12/2010	TCZ 03/2009-08/2009; restart and LI 09/2010 TOC (one infusion) *GC 25mg/d*	**51.8 mg/l**	✞ 2 days after LIP (b); COD: sepsis	>65-70 yrs, female	b) Cardiac arrhythmia, acute abdomen
2	Sigmoidal diverticulitis with abscess, Hansen/Stock State IIb	6/2014	TCZ since 11/2013 LI 06/2014 *GC 5mg/d*	**53 mg/l**	-	>60-65 yrs, Male	Clinical suspicion of sigma diverticulitis
3	Colonic perforation (Colon ascendens)	05/2012	TCZ since 08/2009; LI at 04/2012 *No regular GC; last GC application (once) in November 2011*	**Not known**	-	>75-80 yrs, male	No information about symptoms achievable due to comorbid dementia
4	Covered diverticular perforation of the sigma Comorbidity: Diverticulitis 31.3.-4.4.2013 (TCZ)	04/2014	TCZ 04/12-12/12; 03/13-10/13; Restart 01/14	**< 1 mg/l**	-	>55-60 yrs, female	Abdominal pain since two days, slight nausea and

	Chronic diverticulosis since 2007		LI 03/2014 *GC 7,5 mg/d*				vomiting, no appetite. Soft abdomen, no muscular defense of abdomen
5	Diagnose from death certificate: Perforation of the sigma with subsequent peritonitis of all 4 quadrants Subsequent pneumonia	06/2013	TOC since 03/2013 *GC 15 mg/d*	**n.a.**	✞ 14 days after LIP; COD: pneumonia	>75-80 yrs, female	-
6	Perforation of the sigma with massive purulent peritonitis of all 4 quadrants	04/2014	TOC since 08/2009; LI 4/2014; *GC 5 mg/d*	**19.6 mg/l**	-	>60-65 yrs, female	Diffuse abdominal pain since one week, soft abdomen, no muscular defense of abdomen
7	Ischaemic perforation of colon transversum with peritonitis	01/2012	TOC since 08/2011; LI 12/2011 *GC since 09/2011 increased to 18 mg/d*	**30.5 mg/l**	✞ 12 days after LIP; COD: septic shock with multiorgan failure	>70-75 yrs, female	Sudden severe abdominal pain
8	Transmural perforation of the sigma	05/2009	TOC since 03/2009; LI 04/2009 (2nd TCZ infusion) *GC 15 mg/d*	**72.3 mg/l**	-	>70-75 yrs, female	Slight abdominal pain since several days; sigma perforation was detected with

							sonography at routine rheumatologic visit
9	Perforation of the sigma with peritonitis of all 4 quadrants (only during examination in pathology the diverticulitis was found) Incidental finding in pathology: rectal adenocarcinoma (pT3b, N0 (0/21), L0, V0, R0) – not causing the perforation	04/2014	TOC since 04/2012; LI 04/2014; *GC 5 mg/d*	**20 mg/l**	✞ 3 days after LIP; septic shock	>65-70 yrs, female	Acute abdominal pain
10	Perforation of the sigma	Diagnosed 11/2014	TCZ 02/2012-04/2012 withdrawn because of continuing diarrhoea Restart in 12/2012 LI 09/2014; *No GC (withdrawn since 03/2013 (5 mg/d))*	**11.3 mg/l,** at admission to hospital (27.10.14) increasing to **324.9 mg/l** (4.11.) at transfer to the ICU due to sepsis	✞ 3 months after LIP; COD: cardiac failure	>60-65 yrs, female	Presentation in the clinic with severe back pain (--> trauma surgery); after two days development of severe abdominal pain
	multiple revision surgery	Hospital until 02/2015					
	geriatric rehabilitation	Geriatric rehabilitation in 2/2015					
11	Colonic perforation with acute peritonitis	10/2009	TOC since 05/2009; LI 10/2009; *GC 5 mg/d*	**227.9 mg/l**	✞ 12 days after LIP; COD: escherichia sepsis	>75-80 yrs, female	Abdominal pain since 4 days

LI: last infusion; COD: cause of death; although we have exact dates for age and treatment starts/stops/infusions, we do not show them due to data protection rules

Table S3: Sensitivity analysis with bDMARD naive Control patients.

	Multiple Cox-Regression 1		Multiple Cox-Regression 2	
	HR	95% CI	HR	95% CI
Age at Event (by 5 years)	1.65	[1.36; 1.99]	1.67	[1.37; 2.02]
Sex, males	1.62	[0.78; 3.39]	1.44	[0.69; 2.99]
DMARD (reference: csDMARDs)				
TNFi	1.15	[0.51; 2.60]	1.18	[0.52; 2.65]
Other bDMARDs	0.50	[0.11; 2.24]	0.38	[0.09; 1.68]
Tocilizumab	5.05	[2.15; 11.9]	4.34	[1.83; 10.3]
Glucocorticoids				
Current GC (by 5mg)	1.28	[1.19; 1.39]		
Cumulative GC use[†]			2.01	[1.60; 2.52]
NSAIDs				
Current NSAID	2.22	[1.09; 4.51]		
Cumulative NSAIDs[‡]			2.64	[1.12; 6.21]

In this sensitivity analysis (a) only bDMARD naive patients were included in the reference group of csDMARD patients. Compared to the full analysis this strategy reduced the total number of LIPs to n=32, due to switching treatments.

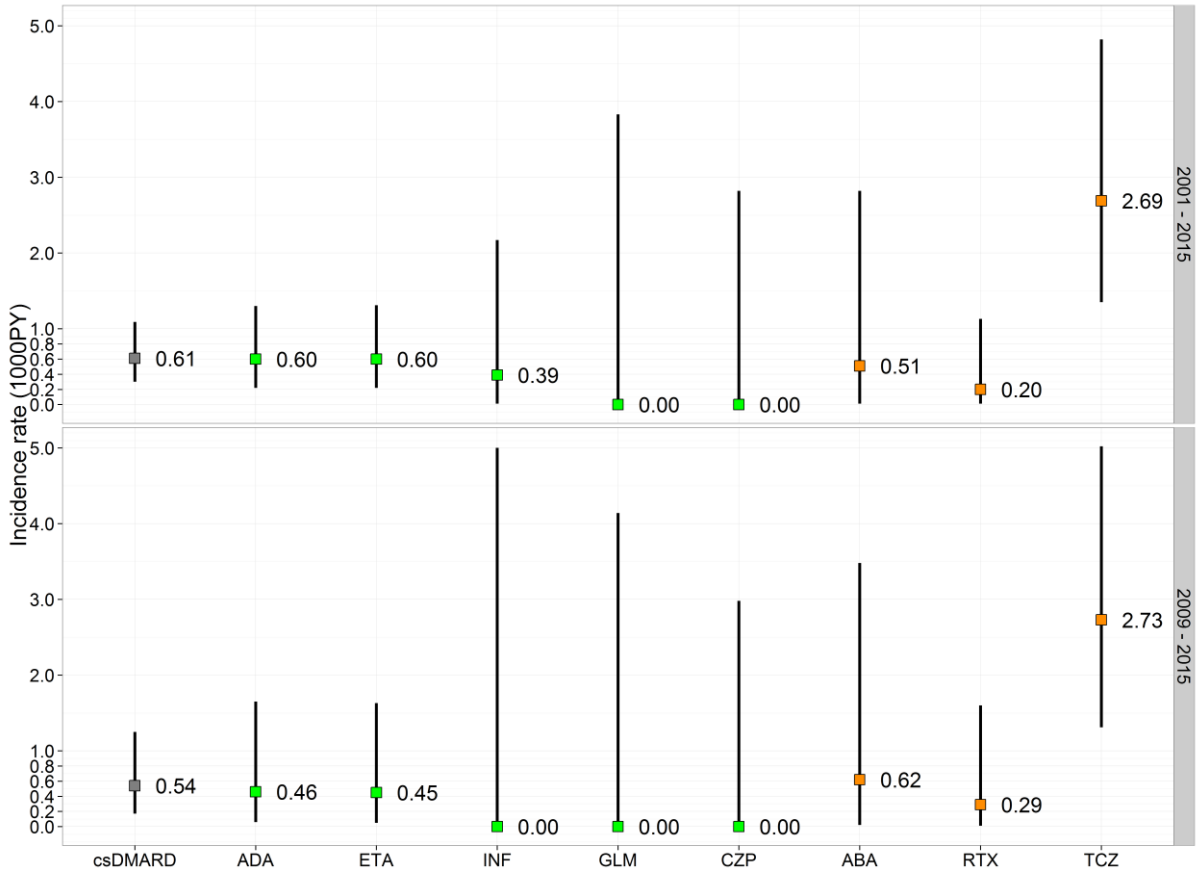
Table S4. Incidence of lower intestinal perforation (LIP) by calendar year.

	2004	2005	2006	2007	2008	2009	2010	2012	2013	2014	2015	
csDMARDs	0	1	1	1	3	1	1	0	1	2	0	**11**
TNFi	2	3	0	3	0	1	1	0	1	2	0	**13**
Tocilizumab	0	0	0	0	0	2	1	2	1	5	0	**11**
Abatacept	0	0	0	0	0	1	0	0	0	0	0	**1**
Rituximab	0	0	0	0	0	0	0	1	0	0	0	**1**
	1	**4**	**1**	**4**	**3**	**5**	**3**	**3**	**3**	**9**	0	**37**

Table S5. Incidence of diverticulitis without perforation by calendar year.

	2004	2005	2006	2007	2008	2009	2010	2012	2013	2014	2015	
csDMARDs	3	0	0	0	2	4	1	3	4	4	2	**23**
TNFi	2	1	1	1	4	1	2	3	2	5	2	**24**
Tocilizumab	0	0	0	0	0	1	0	0	1	2	1	**5**
Abatacept	0	0	0	0	0	0	0	0	0	0	0	**0**
Rituximab	0	0	0	0	0	0	0	1	0	2	0	**3**
	5	**1**	**1**	**1**	**6**	**6**	**3**	**7**	**7**	**13**	**5**	**55**

Figure S1: Incidence rates of lower intestinal perforations (LIP) for csDMARDs and each biologic. The top panel depicts numbers based on all patients enrolled in RABBIT, the lower panel only patients enrolled after 2009 (sensitivity analysis (b)).



Incidence rates and 95% confidence intervals of lower intestinal perforation. Events and Patients years in the top panel: csDMARDs=11/18,113; ADA=6/10,027; ETA=6/9,982; INF=1/2,570; GLM=0/963; CZP=0/1,309; ABA=1/1976; RTX=1/4,950; TCZ=11/4,082. Events and Patients years in the lower panel: csDMARDs=5/9,322; ADA=2/4,379; ETA=2/4,426; INF=0/738; GLM=0/892; CZP=0/1,238; ABA=1/1,602; RTX=1/3,480; TCZ=10/3,660.