Search of Official Nationwide Database in Japan for Adverse Events Associated with Disease-modifying Antirheumatic Drug Therapies: Focus on Therapies in Combination with Methotrexate Author

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Research Article

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Abstract

Disease-modifying antirheumatic drugs (DMARDs) are essential for rheumatoid arthritis (RA) therapy, and many synthetic and biologic drugs are available. DMARDs are frequently prescribed in combination with methotrexate (MTX), as it is the first-line drug. The adverse events (AEs) associated with DMARDs have sometimes unfavorable outcomes. Major AEs, particularly therapies in combination with methotrexate, were investigated in this study. A search of the website of the Japanese Pharmaceuticals and Medical Devices Agency for AEs associated with therapies with five DMARDs (MTX, tacrolimus, adalimumab, tocilizumab, and abatacept) reported from 2014 to 2016 was performed. The AEs searched included lymphoproliferative disease (LPD), cytopenia, interstitial pneumonia (IP), infectious pneumonia other than *Pneumocystis jirovecii* pneumonia (PCP) (i-Pn), and PCP. The number of cases of each AE and its ratio to the total number of cases of all AEs associated with each DMARD therapy were examined. Data were compared among AEs and DMARDs. MTX therapy in combination with other DMARDs was examined for rheumatoid arthritis (RA) cases. On the website, a total of 8874 cases were listed as having AEs associated with therapies with the five DMARDs. For MTX therapy, LPD was the most frequent (1438 cases, 36.4% of all AE cases), followed by cytopenia (10.9%), IP (6.2%), i-Pn (4.1%), and PCP (2.6%). Under therapy with any of the other four DMARDs, i-Pn showed the largest number of cases and the highest ratio (4.2–15.3%); other AEs varied in number and ratio. The proportion of use of MTX in combination with the four DMARDs was highest for PCP (67/71, 94.4%), followed by LPD (50/73, 68.5%), cytopenia (48/73, 65.8%), i-Pn (101/173, 58.4%,), and IP (36/80, 45.0%) (Table 1). In total, including cases reported for MTX therapy, 98.2% (1286/1309) of LPD cases, 88.5% (193/218) of cytopenia cases, 79.8% (174/218) of IP cases, 76.4% (233/305) of i-Pn cases, and 97.6% (165/169) of PCP cases had MTX. In conclusion, LPD was by far the most frequent AE associated with MTX therapy. PCP was strongly associated with the use of MTX in combination with another DMARD. For therapy with any of the other four DMARDs, i-Pn showed the highest ratio.

Introduction

Disease-modifying antirheumatic drugs (DMARDs) are essential for rheumatoid arthritis (RA) therapy, and many synthetic and biologic drugs are available. The administration of DMARDs often causes adverse events (AEs), some of which have unfavorable outcomes. DMARDs are frequently prescribed in combination with methotrexate (MTX) in particular, as it is the first-line drug [1, 2]. Careful evaluation of AEs in association with their use, especially their use in combination with MTX, is important and necessary to minimize AEs.

To investigate AEs associated with DMARDs, postmarketing surveillance (PMS) and registries have been used so far. In this study, the nationwide data available on the website of the official Japanese regulatory agency was adopted, probably for the first time. On the website, the number of cases with an AE and the background information of each case are listed for each drug. With this search, AE cases can be collected from the real world.

Methods

The data source was the website of the Pharmaceuticals and Medical Devices Agency (PMDA) (http://www.info.pmda.go.jp/fsearchnew/jsp/menu_fukusayou_base.jsp). Identifiable personal information is not available in the database.

As a preliminary study, AEs associated with MTX therapy reported from 2014 to 2016 were searched to determine the top five AEs: lymphoproliferative disease (LPD), cytopenia, interstitial pneumonia (IP), infectious pneumonia other than *Pneumocystis jirovecii* pneumonia (PCP) (i-Pn), and PCP (described in Results).

Among all DMARDs covered by the Japan National Health Insurance System, five were selected as representatives: MTX, tacrolimus (TAC), adalimumab (ADA), tocilizumab (TCZ), and abatacept (ABT). For each of these five DMARDs, the total number of AE cases and the number of cases of each AE were obtained, and the ratio of the number of cases of each AE to the total number of cases of all AEs was calculated for each DMARD. The numbers and ratios were compared among AEs and DMARDs.

For individual cases of each AE, only those with RA were included for further analysis. For each RA case with an AE associated with the four DMARDs excluding MTX, therapy in combination with MTX was investigated. For the LPD cases that were not associated with MTX therapy, a combination of DMARDs other than the four was examined. For i-Pn cases with RA treated with ABT, which has been launched in the market most recently, the annual change in their number was examined. For PCP cases associated with MTX therapy, MTX use in combination with other DMARDs, steroids, and prophylactic therapy with trimethoprim–sulfamethoxazole combination or pentamidine (ST), and their outcomes were also investigated.

A literature search of the proportion of MTX use in combination with each of the other four DMARDs as assessed in PMS was conducted. Statistical analysis was carried out using Fisher's exact test, and $p < 0.05$ was considered statistically significant. In this research, there was no direct involvement with patients or the public. This study was approved by the Ethics Committee of Chiba Central Medical Center with the approval number H30-R18.

Results

On the PMDA website, a total of 8874 cases were listed as having AEs associated with therapies with the five DMARDs. As cases with AEs observed to be associated with MTX therapy, 3955 cases were reported from 2014 to 2016. These comprised 1438 LPD cases, 432 cytopenia cases, 245 IP cases, 162 i-Pn cases, 101 PCP cases, 37 tuberculosis cases, 37 hepatitis B cases, and others (Fig. 1). Among these, the top five were focused on in this study, and the following results apply to these AEs associated with each of the five DMARDs.

The number of AE cases for each DMARD is shown in Table 1 and Fig. 1. The number of cases of a specific AE and all other AEs for each DMARD, and the ratio of the number of cases of an AE to the total number of cases of all AEs are shown in Fig. 2 and Table 1. For each specific AE, its ratio differed significantly among the five DMARDs ($p < 0.001$).

Table 1
Ratios of numbers of cases with an AE to total numbers of all AE cases, and RA cases with an AE with and without MTX in combination with other DMARDs.

		All cases		**RA cases**				
AE	DMARD				Combination MTX			
		Cases including RA and others	Ratio to total number of cases with all AEs*	RA cases	+	-	No available data	Proportion of MTX use in cases with available data
		(n)	(%)	(n)	(n)	(n)	(n)	(%)
LPD								
	ABT	18**	3.2	20**	13	3	4	81.2
	ADA	27	2.9	16	12	2	2	85.7
	TCZ	22	1.5	26	7	9	10	43.8
	TAC	53	2.7	34	18	9	7	66.7
	MTX	1438	36.4	1236	1236	/	/	/
	All 5 DMARDs	*1558*	*/*	*1332*	*1286*	*23*	*/*	*98.2*
Cytopenia								
	ABT	10	1.8	9	4	4	1	50
	ADA	43	4.5	12	10	1	1	90.9
	TCZ	90	6.2	59	31	14	14	68.9
	TAC	75	3.8	12	3	6	3	33.3
	MTX	432	10.9	145	145	/	/	/
	All 5 DMARDs	*650*		*237*	*193*	*25*	*/*	*88.5*
IP								
	ABT	29	5.2	28	6	12	10	33.3
	ADA	42	4.4	15	11	2	2	84.6
	TCZ	45	3.1	50	14	19	17	42.4

		All cases		RA cases				
	TAC	44	2.2	24	5	11	8	31.3
	MTX	245	6.2	138	138	/	/	/
	All 5 DMARDs	*405*		*255*	*174*	*44*	*/*	*79.8*
i-Pn								
	ABT	85	15.3	72	34	19	19	64.2
	ADA	63	6.7	20	16	1	3	94.1
	TCZ	122	8.4	115	38	26	51	59.4
	TAC	82	4.2	45	13	26	6	33.3
	MTX	162	4.1	132	132	/	/	/
	All 5 DMARDs	*514*	*/*	*384*	*233*	*72*	*/*	*76.4*
PCP								
	ABT	25	4.5	25	18	3	4	85.7
	ADA	35	3.7	27	26	0	1	100
	TCZ	25	1.7	21	15	1	5	93.8
	TAC	24	1.2	8	8	0	0	100
	MTX	101	2.6	98	98	/	/	/
	All 5 DMARDs	*210*	*/*	*179*	*165*	*4*	*/*	*97.6*

*AE cases for each DMARD are shown in Fig. 1. **Confirmed for discrepancy. AE, adverse event; DMARD, disease-modifying antirheumatic drugs; RA, rheumatoid arthritis; MTX, methotrexate; ABT, abatacept; ADA, adalimumab; TCZ, tocilizumab; TAC, tacrolimus; LPD, lymphoproliferative disease; IP, interstitial pneumonitis; i-Pn, infectious pneumonitis other than PCP; PCP, *Pneumocystis jirovecii* pneumonia

In the results that follow, no significant differences in the ratio of cases of an AE was found between any of two DMARDs unless specified. p Value is shown in Results only in the case of $p < 0.005$.

On the webpage, there were occasional discrepancies in the numbers listed in the case number page compared with the case presentation page. There were also blank columns for some cases. Information on the dosage of either MTX or the four DMARDs was not available in most cases. Almost all of the cases were reported by pharmaceutical companies.

LPD

Among the AEs, the number of LPD cases (1438) and its ratio (36.4%) were extremely high for MTX (as shown above, Table 1, Figs. 1 and 2), most of which were indicated for RA therapy (1236/1438). Among the other four DMARDs, the LPD ratio for ABT was higher than that for TAC or TCZ, the ratio for ADA was higher than that for TCZ, and the ratio for TAC was higher than that for TCZ. TCZ showed the lowest LPD ratio of 1.5%.

MTX was used in combination with ADA in 2/14 cases, with ABT in 13/16 cases, with TAC in 18/27 cases, and with TCZ in 7/16 cases (Table 1, Fig. 3). For all of the four DMARDs excluding MTX, the proportion of their use in combination with MTX was 68.5% (50/73). In total, including cases reported for MTX therapy, 98.2% (1286/1309) had MTX.

As for the cases of LPD not associated with MTX, various combinations of DMARDs were observed, including the combinations of TAC and ABT, and TAC and salazosulfapyridine in three cases each.

Cytopenia

Among the five DMARDs, the number of cytopenia cases (432) and its ratio to the total number of cases of all AEs were the highest for MTX therapy (10.9%), followed by TCZ, ADA, TAC, and ABT (which showed the lowest ratio, 1.8%) therapies (Table 1, Fig. 2). The ratio was significantly higher for MTX than for any of the other four DMARDs ($p < 0.001$). For all of the four DMARDs excluding MTX, the proportion of their use in combination with MTX was 65.8% (48/73).

In total, including reported cases with MTX therapy, 88.5% (193/218) had MTX.

IP

The ratio of IP cases to the total number of cases of all AEs was the highest for MTX therapy (6.2%, Fig. 2, Table 1), but was not significantly different from that for ABT therapy (5.2%), which showed the second highest ratio. TAC therapy showed the lowest ratio of IP cases (2.2%) among the five DMARDs, and the second lowest among AEs associated with TAC therapy (Fig. 1).

The number of IP cases associated with ABT therapy without MTX was smaller than that for ABT used in combination with MTX (6 vs. 12, Table 1). As for ADA therapy, therapy in combination with MTX was used in 11/13 of IP cases; a similar trend was observed for each AE associated with ADA (Fig. 3) and in PMS. MTX in combination with the other four DMARDs accounted for 45.0% (36/80) of the cases, and MTX use in total accounted for 79.8% (174/218) of all IP cases (Table 1, Fig. 3).

i-Pn

MTX showed the lowest i-Pn ratio among the five AEs (162/3955, Fig. 2, Table 1). On the other hand, for all the other four DMARDs, the number and ratio of i-Pn cases were the highest among the five AEs (Fig. 1). Among the therapies with the five DMARDs, ABT showed the highest i-Pn ratio (85/556, Fig. 2).

The annual numbers of i-Pn cases for ABT were 17 in 2014, 29 in 2015, and 37 in 2016. TCZ had the second highest i-Pn ratio (122/1455), followed by ADA and TAC (Fig. 2).

The numbers of i-Pn cases associated with MTX in combination with the other four DMARDs were 16/17 for ADA, 34/53 for ABT, 38/64 for TCZ, and 13/39 for TAC; MTX use accounted for 58.4% (101/173). In total, MTX was used in 76.4% (233/305) of all i-Pn cases (Table 1, Fig. 3).

PCP

There were 210 PCP cases reported in total for the five DMARDs, among which 101 were reported for MTX (Table 1, Fig. 1), out of which 98 had RA (Table 1, Fig. 3). For the other four DMARDs, 81 RA cases were reported to also develop PCP. The ratio of the number of PCP cases to the total number of all AEs cases was the highest for ABT, followed by ADA (Fig. 2).

Among the 81 RA cases associated with the other four DMARDs, 71 had available data for their use in combination with MTX, among which 67 (94.4%) had MTX (Table 1, Fig. 3). The ratio of PCP cases associated with the other four DMARDs used in combination with MTX was significantly higher than those of cytopenia, IP, or iPn cases ($p < 0.001$, Fig. 3). This ratio was not different between PCP cases and LPD cases ($p = 0.538$). In total, MTX was administered in 165 out of 169 (97.6%) RA cases with PCP.

Of the 98 RA cases that developed PCP associated with MTX, 63 had available data on the use of combinations of DMARDs, and 43 (68.3%) showed the use of another DMARD. Among 134 (71 + 63) RA cases with available data on the use of MTX in combination with another DMARD, 110 (67 + 43, 82.1%) showed the use of combination therapy. The 63 cases associated with MTX described above were also investigated for the use of combinations of drugs other than DMARDs, and 48 (76.2%) showed the use of a steroid, and 62 (98.4%) had either a steroid or a DMARD other than MTX. A prophylactic medicine was prescribed in 11 out of 150 (7.3%) PCP cases with available data: 4/76 (5.3%) for MTX, 0/21 for ABT, 2/27 for ADA, 3/18 for TCZ, and 2/8 for TAC. The outcomes were 21 deaths (14.6%) and 123 recoveries, whereas no data were available for 35 cases.

Taking together the data on MTX use in all these cases, MTX was significantly more frequently used in LPD and PCP cases than in either cytopenia, IP, or i-Pn cases. The proportion of MTX use was not significantly different between LPD and PCP cases (Table 1). However, for the four DMARDs excluding MTX, the ratio of PCP cases associated with their use in combination with MTX was significantly higher (67/71) than that of LPD cases (50/73) ($p < 0.001$).

Combination MTX in comparison with that in PMS

MTX used in combination with one of the four DMARDs in PMS after their launch in the market is summarized in Table 2 [3–6]. The following include AEs associated with MTX used in combination with the other DMARDs with a significantly different ratio from those in PMS, and also those without a significantly different ratio.

Table 2
MTX in combination with the four DMARDs in postmarketing surveillance

	n	Duration	Reference	Combination with MTX (%)
ABT	3882	2010/09–2011/06	Mod Rheumatol 2016;26:491	66.3
ADA	7740	2008/06–2010/10	Mod Rheumatol 2015;25:495	74.9
TCZ	7901	2008/04–2010/08	J Rheumatol 2014;41:15	55.8
TAC	3172	2005/04–2009/03	Mod Rheumatol 2014;24:8	28.9
Abbreviations as indicated in Table 1.				

In LPD cases associated with TAC therapy, the proportion of its use in combination with MTX was significantly higher than in PMS ($p < 0.001$); the ratio of two-thirds was higher than that (less than one-third) observed in PMS (Table 2). MTX was significantly more frequently used for PCP cases in combination with ADA ($p < 0.005$), TCZ ($p < 0.005$), and TAC therapies ($p < 0.001$) (Table 2, Fig. 3) than in PMS. For ABT therapy, the proportion of its use in combination with MTX was also higher in PCP cases, but not significantly (18/21 vs. 2574/3882, $p = 0.060$).

In cytopenia cases, MTX was frequently used in combination with ADA (9/10) and TCZ (31/45) (Table 1, Fig. 3), whose ratios were higher than those in PMS (Table 2), but not significantly. As for ADA therapy, therapy in combination with MTX was used in 11/13 of IP cases; a similar trend was observed for each AE associated with ADA (Fig. 3) and in PMS. In IP cases associated with ABT therapy, the proportion of its use in combination with MTX was significantly lower than that in PMS ($p < 0.005$). In iPn cases, MTX uses in combination with ABT (34/53), ADA (16/17), TCZ (38/64) and TAC were not significantly different from those in PMS.

Discussion

In this study, 8874 cases of AEs associated with therapies with five major DMARDs were analyzed. The data source was the webpage of PMDA. PMDA was established in 2004 under the law as the safety information reporting system, in which medical professionals working at an institution or a pharmaceutical company shall report the occurrence of any AEs as per regulatory requirements. On the webpage are posted the number of AE cases and case records for each drug, every quarter. In the case records, the underlying disease or indication, combinations of drugs, and outcomes of AEs are available. This is the first report based on a search of this valuable nationwide database.

In Japan, over 20 DMARDs are available. MTX has always been the first-line drug for therapy, whereas TAC has been increasingly prescribed as a conventional synthetic DMARD in Japan. Among biologic DMARDs that were widely used from 2014 to 2016 in Japan, ADA was the major antitumor necrosis factor drug, TCZ was the only anti-IL6 drug, and ABT was the only anti-CTLa4-IgGFc drug. These five DMARDs were investigated in this study. The indications for the four DMARDs excluding ABT covered by the Japan Health Insurance System include diseases other than RA; ABT is only for RA.

One of the major concerns in the clinical use of DMARDs is AE occurrence. The relationship of an AE with each DMARD can be estimated by comparing the ratio of that AE with the ratios of other AEs for each DMARD and by comparing the ratio of that AE among DMARDs. Because over 70% of RA patients are given MTX alone or in combination with other DMARDs [7, 8], such combination should also be considered. These could be studied only with such extensive data provided by PMDA. The proportion of the use of MTX in combination with another DMARD being clearly higher than that in PMS was also considered meaningful.

The proportion of AEs associated with MTX therapy was noteworthy in that the ratio of the number of LPD cases to the total number of cases of all AEs was extremely high. For the other four DMARDs, the ratio of LPD cases was far lower (Table 1, Fig. 2), and MTX was used in combination in two-thirds of the cases (Fig. 3). For TCZ, the ratio of LPD cases was the lowest (Fig. 2), and MTX was used in combination with TCZ only in a few cases in this search and in PMS. Taking these findings into consideration, MTX involvement in LPD development is highly plausible, whereas LPD might not easily develop in therapies with only one of the other four DMARDs.

There have been no comparative studies of the ratio of LPD cases to the total number of all AE cases or among DMARDs in the literature. A report from Japan described the cases of four patients with LPD associated with MTX therapy, with an incidence of 0.00168/person-year [9]. Another report of a case control study of 28 MTX–LPD and 125 MTX–non-LPD RA patients revealed higher MTX dose as an independent risk factor [10]. It is shown that the prevalence of Epstein–Barr virus infection, which has been associated with a remarkably diverse range of lymphomas [11], differs among countries, and most Japanese become Epstein–Barr-virus-antibody-positive in their young age [12].

There is a possible association of cytopenia with MTX, as a significantly higher ratio among all AEs was found for MTX than for any of the other four DMARDs (Fig. 2). Moreover, in cytopenia cases associated with TCZ and ADA therapies, the proportions of use of these therapies in combination with MTX were higher than those in PMS (Table 2, Fig. 3). However, for MTX, both the number of cases of cytopenia and its ratio to the total number of all AEs cases were much lower than those of LPD, suggesting that the association of MTX with cytopenia development was weaker than that with LPD.

There is no consensus in the literature regarding the association of the use of these DMARDs in combination with MTX with cytopenia. The concomitant use of MTX or TCZ with an intravenous biologic DMARD is a predictor of neutropenia [13]. The use of a nonsteroidal anti-inflammatory drug with MTX was a risk factor for cytopenia [14]. The concomitant use of ST was not associated with cytopenia [15]. MTX has limited drug interactions except that ST and high-dose acetylsalicylic acid can exacerbate toxicity, but DMARDs other than MTX were not among the drugs searched [16]. Only 30% of cases with MTX-related myelosuppression were treated with other DMARDs [17].

IP was the third most frequent AE associated with MTX therapy. However, for ABT, TCZ, or TAC therapy, the proportion of its use in combination with MTX was less than half of that in IP cases (Table 1). MTX association with IP development appeared weaker than that with LPD and cytopenia.

Unexpectedly, the ratio of IP cases to the total number of cases of all AEs was the lowest for TAC therapy, considering that immediately after the launch of TAC in the market in 2005, severe IP was reported particularly in cases with pre-existing lung diseases [18, 19]. It is possible that TAC administration in such high-risk cases has been avoided since then, resulting in a low ratio of IP cases during the study period. In the literature, a large cohort case study of biologic DMARDs showed that MTX rather reduced hospitalization due to IP [20]. A safety cohort study of 157 RA patients treated with ADA in combination with MTX revealed that this therapy was associated with five AEs including IP and PCP [21]. No risk factors were identified for IP associated with MTX [22].

i-Pn showed the highest ratio among the five AEs for all of the four DMARDs other than MTX (Table 1, Fig. 1). Among the four DMARDs, ABT showed the highest ratio of i-Pn cases (Fig. 2), which was unexpected as ABT has been considered to be safer with a low incidence of AEs [23]. This might paradoxically account for its high ratio, as ABT might have been increasingly given preferentially to patients with risk factors during the study period that started five months after its launch in the market.

The ratio of i-Pn cases associated with MTX therapy was the lowest among the five DMARDs (Fig. 2). As for the use of MTX in combination with the other DMARDs, although a high proportion of i-Pn cases was associated with ADA and MTX combination therapy, this was similarly observed for all the five AEs studied (Fig. 3) and in PMS (Table 2).

In this study, one of the novel and important findings is that PCP development was strongly associated with MTX therapy in combination with another DMARD. In addition to the fact that over 97% of PCP cases were associated with MTX therapy, over 82% with available data showed the use of MTX and another DMARD in combination.

As for 3955 cases of AEs associated with MTX therapy, the ratio of PCP cases was only the fifth highest among all AEs (Fig. 1); this ratio was even lower than that for ABT or ADA therapy (Fig. 2). Among PCP cases associated with MTX therapy, two-thirds (43/63) showed the use of other DMARDs in combination. For ABT or ADA therapy, the ratio of PCP cases and the proportion of use of MTX in combination with these drugs were high both in this search (Figs. 2 and 3) and in PMS (Table 2). Hence, another DMARD in combination with MTX might be meaningful. Prophylactic ST was used in only 7% of PCP cases. As the mortality rate was high (14.6%), patients treated with a DMARD in combination with MTX should be monitored for PCP development.

There have been previous reports indicating MTX as a risk factor for PCP, even in small patient cohorts. A report of 19 patients and controls showed MTX ≧ 6 mg/week as a risk factor [24]. Another report of 60 cases and controls showed that sulfasalazine decreased the risk of PCP, and without it, MTX increased the risk with an odds ratio of 5.25 [25]. In contrast to these reports, in the present study, large numbers of PCP cases (179 including 81 associated with the four DMARDs other than MTX) were examined, and MTX in combination with other DMARDs was focused on.

This study was unique in its focus on MTX in combination with other DMARDs for each AE. The comparison revealed greater or lesser degrees of MTX involvement in the development of a specific AE. In addition, the use of the nationwide public database was an important novel method.

Study limitations include the following. Reporting bias is unavoidable; even though officially required, the report is entrusted to medical practitioners and mainly pharmaceutical companies. Only five DMARDs and only the top five AEs associated with MTX therapy were investigated. Results cannot be compared with those of cases without any AE. Literature reviews comprised mostly reports from Japan.

In conclusion, LPD was the remarkably frequent AE associated with MTX therapy in Japanese RA patients. Cytopenia was weakly associated with MTX therapy compared with LPD. Almost no association of IP with MTX in combination with other DMARDs was observed. i-Pn developed with the highest ratio for any of the other four DMARDs excluding MTX, and with the lowest ratio for MTX. PCP development was strongly associated with MTX therapy in combination with other DMARDs.

Declarations

Competing interest

The author has no competing interests in relation to this study.

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Ethics approval

Approved by the Ethics Committee of Chiba Central Medical Center

with the approval number H30-R18.

Author contribution

Single author was involved throughout this study.

Data availability

Data are available in PMDA website:
http://www.info.pmda.go.jp/fsearchnew/jsp/menu_fukusayou_base.jsp

References

1. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biologic disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis.* 2017;76:960–977.
2. Kameda H, Fujii T, Nakajima A, Koike R, Sagawa A, Kanbe K, et al. Japan College of Rheumatology guideline for the use of methotrexate in patients with rheumatoid arthritis. *Mod Rheumatol.* 2018 May 24(E-pub ahead of print).
3. Harigai M, Ishiguro N, Inokuma S, Mimori T, Ryu J, Takei S, et al. Postmarketing surveillance of the safety and effectiveness of abatacept in Japanese patients with rheumatoid arthritis. *Mod Rheumatol.* 2016;26:491–498.
4. Yamanaka H, Harigai M, Ishiguro N, Inokuma S, Takei S, Takeuchi T, et al. Trend of patient characteristics and its impact on the response to adalimumab in patients with rheumatoid arthritis: post hoc time-course analysis of an all-case PMS in Japan. *Mod Rheumatol* 2015;25:495–502.
5. Saeki Y, Matsui T, Saisho K, Tohma S. Current treatments of rheumatoid arthritis: from the 'NinJa' registry. *Expert Rev Clin Immunol.* 2012;8:455–465.
6. Yamanaka H, Seto Y, Tanaka E, Furuya T, Nakajima A, Ikari K, et al. Management of rheumatoid arthritis: the 2012 perspective. *Mod Rheumatol.* 2013;23:1–7.
7. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, et al. Effectiveness and safety of tocilizumab: Postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. *J Rheumatol.* 2014;41:15–23.
8. Takeuchi T, Kawai S, Yamamoto K, Harigai M, Ishida K, Miyasaka N, et al. Post-marketing surveillance of the safety and effectiveness of tacrolimus in 3,267 Japanese patients with rheumatoid arthritis. *Mod Rheumatol.* 2014;24:8–16.
9. Yoshida Y, Takahashi Y, Yamashita H, Kano T, Kaneko H, Mimori A, et al. Clinical characteristics and incidence of methotrexate-related lymphoproliferative disorders of patients with rheumatoid arthritis. *Mod Rheumatol.* 2014;24:763–765.
10. Kameda T, Dobashi H, Miyatake N, Inoo M, Onishi I, Kurata N, et al. Association of higher methotrexate dose with lymphoproliferative disease onset in rheumatoid arthritis patients. *Arthritis Care Res (Hoboken).* 2014;66:1302–1309.
11. Vockerodt M, Yap LF, Shannon-Lowe C, Curley H, Wei W, Vrzalikova K, et al. The Epstein–Barr virus and the pathogenesis of lymphoma. *J Pathol.* 2015;235:312–22.
12. Kusuhara K, Takabayashi A, Ueda K, Hidaka Y, Minamishima I, Take H, et al. Breast milk is not a significant source for early Epstein–Barr virus or human herpesvirus 6 infection in infants: a seroepidemiologic study in 2 endemic areas of human T-cell lymphotropic virus type I in Japan. *Microbiol Immunol.*1997;41:309–312.
13. Espinoza F, Le Blay P, Combe B. Biologic disease-modifying antirheumatic drug (bDMARD)-induced neutropenia: A registry from a retrospective cohort of patients with rheumatic diseases treated with 3

classes of intravenous bDMARD. *J Rheumatol.* 2017 Jun;44(6):844-849.

14. Svanström H, Lund M, Melbye M, Pasternak B. Combination use of low-dose methotrexate and NSAIDs and the risk of serious adverse events among patients with rheumatoid arthritis. *Pharmacoepidemiol Drug Saf.* 2018;27:885–893.
15. Kwon OC, Lee JS, Kim YG, Lee CK, Yoo B, Hong S. Safety of the combination use of methotrexate and a prophylactic dose of trimethoprime-sulfamethoxazole. *J Rheumatol.* 2017;44:844–849.
16. Bourré-Tessier J, Haraoui B. Methotrexate drug interactions in the treatment of rheumatoid arthritis: a systematic review. *J Rheumatol.* 2010;37:1416–1421.
17. Mori S, Hidaka M, Kawakita T, Hidaka T, Tsuda H, Yoshitama T, et al. Factors associated with myelosuppression related to low-dose methotrexate therapy for inflammatory rheumatic diseases. *PLoS One.* 2016;11:e0154744.
18. Miwa Y, Isozaki T, Wakabayashi K, Odai T, Matsunawa M, Yajima N, et al. Tacrolimus-induced lung injury in a rheumatoid arthritis patient with interstitial pneumonitis. *Mod Rheumatol.* 2008;18:208–211.
19. Sasaki T, Nakamura W, Inokuma S, Matsubara E. Characteristic features of tacrolimus-induced lung disease in rheumatoid arthritis patients. *Clin Rheumatol.* 2016;35:541–545.
20. Curtis JR, Sarsour K, Napalkov P, Costa LA, Schulman KL. Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor α agents, a retrospective cohort study. *Arthritis Res Ther.* 2015;17:319.
21. Ito Y, Hozumi K, Okada Y, Kurimoto S. Adalimumab with methotrexate in treatment-naïve Japanese patients with rheumatoid arthritis at risk of progressive structural joint damage: A postmarketing observational study. *Rheumatol Ther.* 2017;4:151–166.
22. Sathi N, Chikura B, Kaushik VV, Wiswell R, Dawson JK. How common is methotrexate pneumonitis? A large prospective study investigates. *Clin Rheumatol.* 2012;31:79–83.
23. Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis.* 2008; 67:1096–1103.
24. Yukawa K, Nagamoto Y, Watanabe H, Funaki M, Iwahashi M, Yamana J, et al. Risk factors for *Pneumocystis jirovecii* pneumonia in patients with rheumatoid arthritis and a prophylactic indication of trimethoprim/sulfamethoxazole. *Clin Rheumatol.* 2018 Apr 17 (E-pub ahead of print)
25. Nunokawa T, Yokogawa N, Shimada K, Sugii S, Nishino J, Gosho M, et al. Prophylactic effect of sulfasalazine against *Pneumocystis* pneumonia in patients with rheumatoid arthritis: A nested case-control study. *Semin Arthritis Rheum.* 2018 Jun 13 (E-pub ahead of print).

Figures

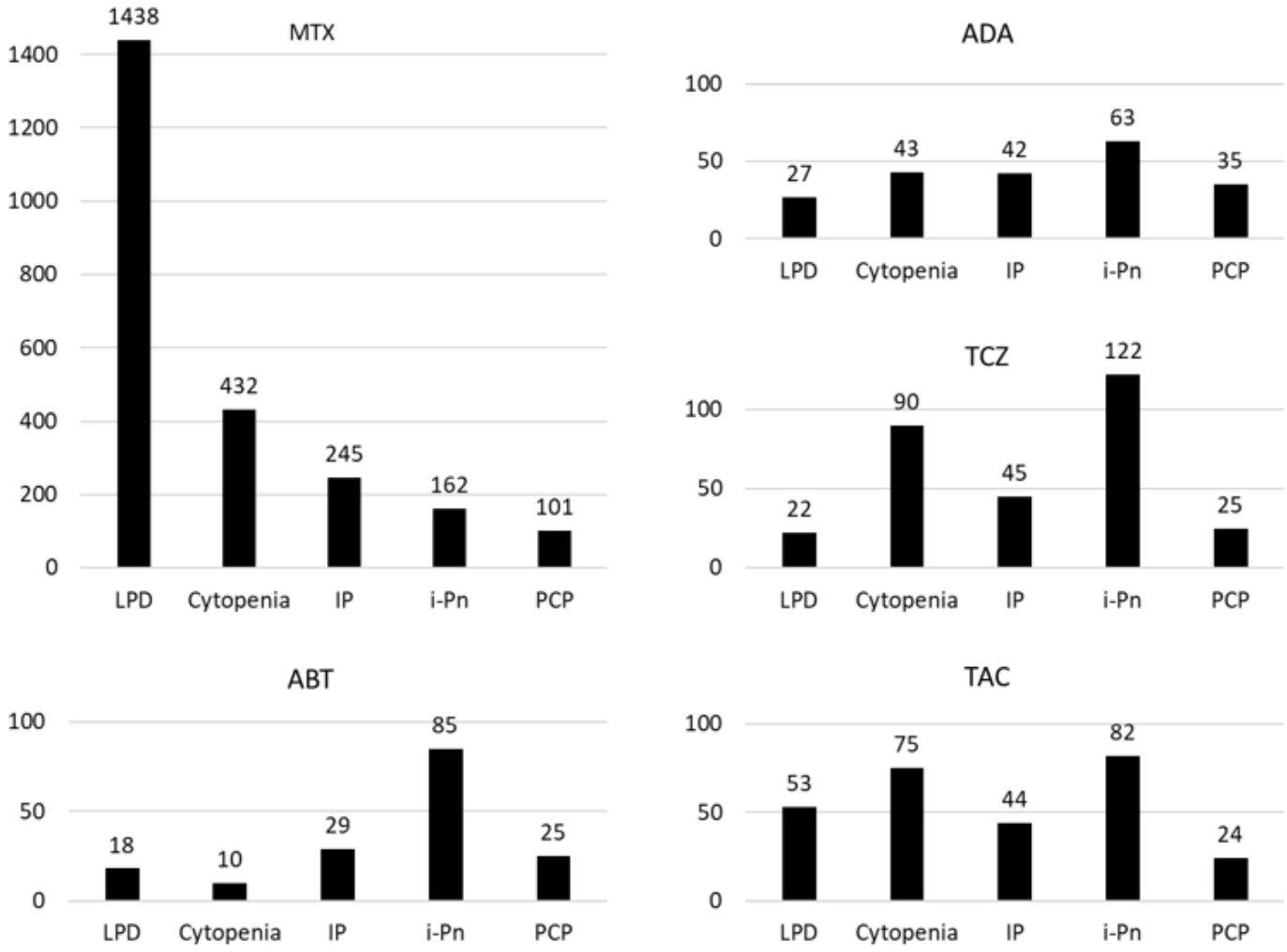

Figure 1

All cases, including those with diseases other than RA, with an AE associated with each DMARD. MTX, methotrexate; ABT, abatacept; ADA, adalimumab; TCZ, tocilizumab; TAC, tacrolimus; LPD, lymphoproliferative disease; IP, interstitial pneumonia; i-Pn, infectious pneumonia other than Pneumocystis jirovecii pneumonia (PCP).

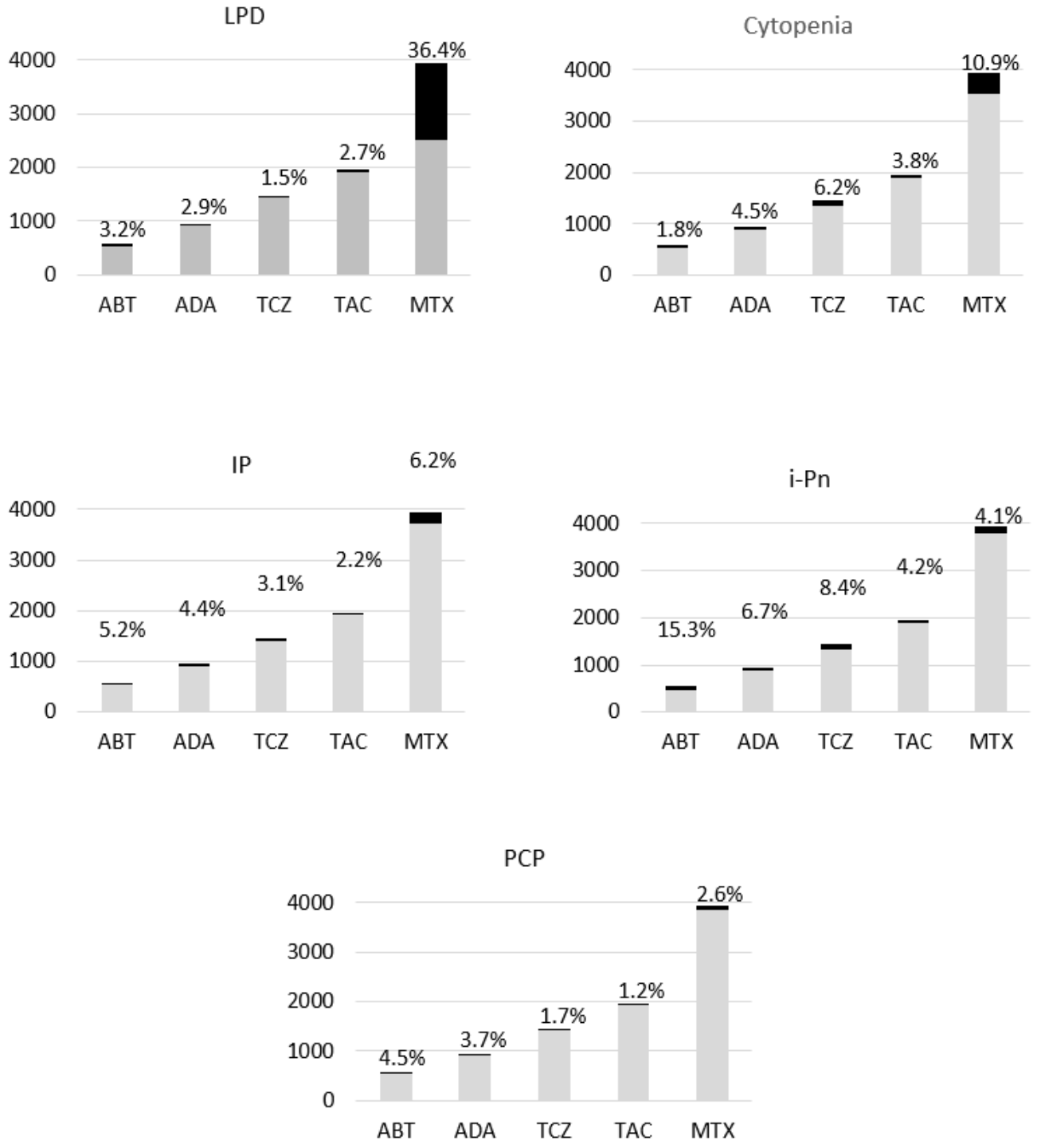

Figure 2

Cases with specified AE (black) and cases of AEs other than that (gray) associated with a DMARD. Abbreviations as indicated in the legend of Fig. 1.

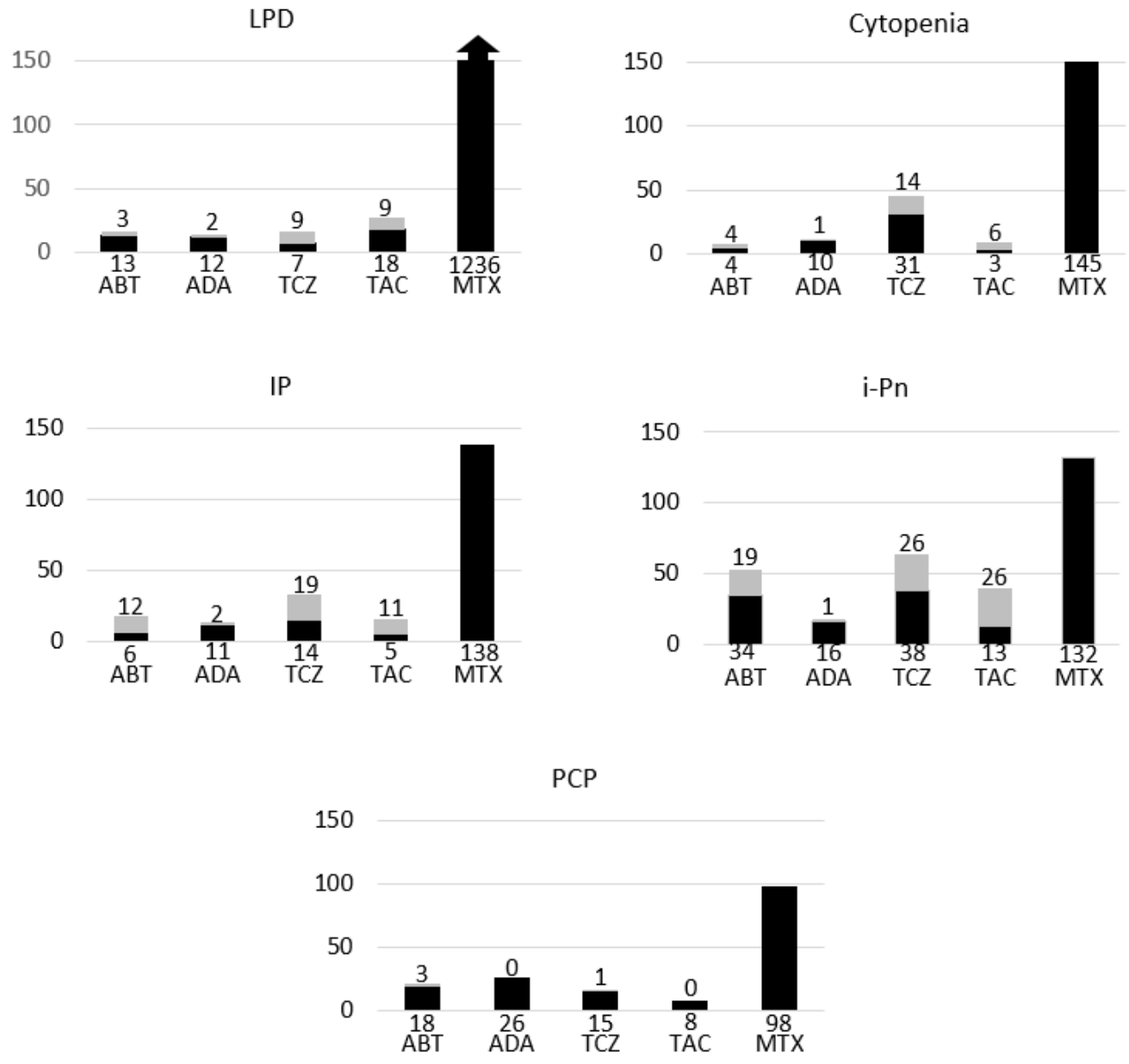

Figure 3

RA cases that developed an AE with (black) and without (gray) MTX in combination with other DMARDs. Abbreviations as indicated in the legend of Fig. 1.