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Pulmonary Adverse Events of Low-Dose Methotrexate in the Randomized, Double-Blind, Placebo-Controlled Cardiovascular Inflammation Reduction Trial

Jeffrey A. Sparks, Paul F. Dellaripa, Robert J. Glynn, Nina P. Paynter, Chang Xu, Paul M. Ridker, and Daniel H. Solomon

大村　浩一郎

MTXによる薬剤性肺炎の頻度はどのくらいか？

RAにおける観察研究とそのメタ解析がほとんど

・21のprospective studies (MTX monotherapy 2年以上。平均観察期間36.5か月）でMTX肺炎は0.43% (15/3463) だった。比較解析なし。

(Salliot C, van der Heijde D. Ann Rheum Dis 2009; 68: 1100)

・肺臓炎の記載のある4つのRCT(24週以上観察、100例以上)のメタ解析でMTX肺炎の頻度は1.16% (13/1125) で、リスクはRR 7.81 (95% CI: 1.76-34.72)だった。

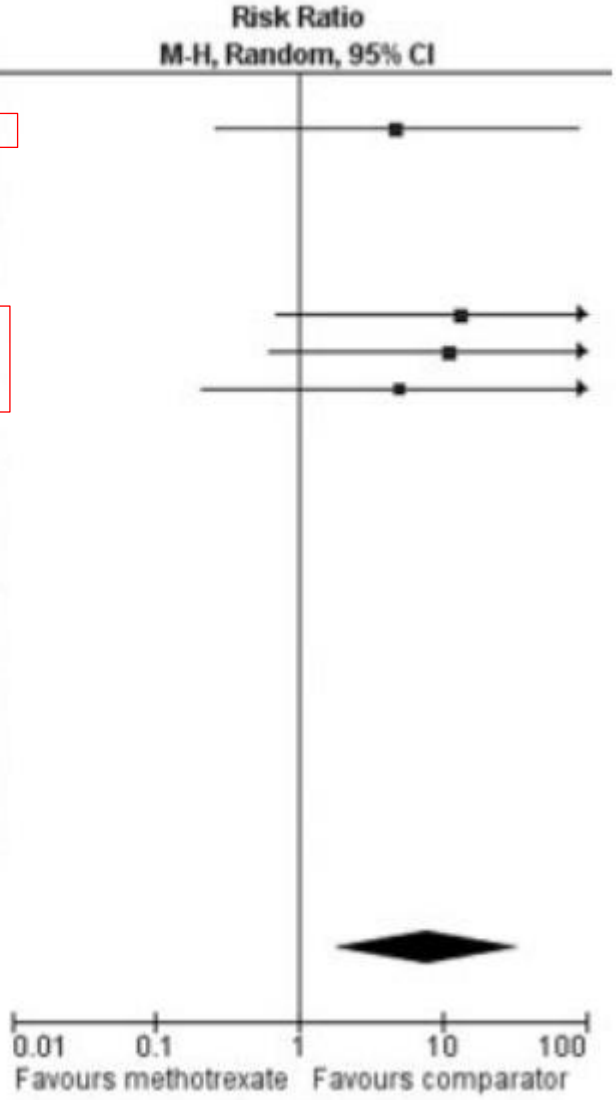
(Conway R. et al., Arthritis Rheumatol 2014; 66: 803)

文献2のMTX-IPのRR meta解析データ

Study or Subgroup	Methotrexate Events	Total	Comparator Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Weinblatt et al, 1990	0	138	0	142		Not estimable	1990
Williams et al, 1992	4	220	0	115	26.2%	4.72 [0.26, 86.99]	1992
O'Dell et al, 1996	0	67	0	35		Not estimable	1996
Boers et al, 1997	0	76	0	79		Not estimable	1997
Haagsma et al, 1997	0	71	0	34		Not estimable	1997
Rau et al, 1997	0	87	0	87		Not estimable	1997
Bathon et al, 2000	3	217	0	415	25.4%	13.36 [0.69, 257.43]	2000
Emery et al, 2000	5	498	0	501	26.6%	11.07 [0.61, 199.60]	2000
Cohen et al, 2001	1	190	0	318	21.8%	5.01 [0.21, 122.38]	2001
Edwards et al, 2004	0	80	0	81		Not estimable	2004
Breedveld et al, 2006	0	525	0	274		Not estimable	2006
van der Heijde et al,2006	0	459	0	223		Not estimable	2006
Nishimoto et al, 2007	0	145	0	157		Not estimable	2007
Zhang et al, 2008	0	106	0	105		Not estimable	2008
Emery et al, 2009	0	478	0	159		Not estimable	2009
Hu et al, 2009	0	118	0	120		Not estimable	2009
Lu et al, 2009	0	163	0	326		Not estimable	2009
Nishimoto et al, 2009	0	64	0	61		Not estimable	2009
Wei et al, 2009	0	158	0	296		Not estimable	2009
Jones et al, 2010	0	284	0	288		Not estimable	2010
Keystone et al, 2010	0	311	0	133		Not estimable	2010
Ishaq et al, 2011	0	89	0	91		Not estimable	2011
Total (95% CI)		**4544**		**4040**	**100.0%**	**7.81 [1.76, 34.72]**	
Total events	13		0				

Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 3 (P = 0.95); I² = 0%

Test for overall effect: Z = 2.70 (P = 0.007)



Conway R. et al., Arthritis Rheumatol 2014; 66: 803

β-Dグルカンの日本での保険適応は1995年　　FDA認可は2004年⇨ PCPが混じっている可能性

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副作用発現率は 28.1%（27/96 例、40 件）であった。副作用全体の 45.0%（18/40 件）が消化器症状であった。また、重度の副作用は間質性肺炎であり 2.5%（2/40 例、1 件）に見られた。投与中止例又は脱落例は 70/96 例（72.9%）にみられた。理由は、「本剤による有害事象・副作用又は臨床検査値異常」が 19 例（19.8%）、「症状の悪化又は不変」が 8 例（8.3%）、「症状改善により治療不要となった」が 1 例（1.0%）であった。

(2) 重大な副作用と初期症状

7) 間質性肺炎（0.1～5%未満）、肺線維症（0.1%未満）、胸水（頻度不明）

間質性肺炎、肺線維症、胸水等があらわれ、呼吸不全にいたることがあるので、観察を十分に行い、発熱、咳嗽、呼吸困難等の呼吸器症状があらわれた場合には、速やかに胸部 X 線等の検査を行い、本剤の投与を中止するとともに副腎皮質ホルモン剤の投与等の適切な処置を行うこと。

3 間質性肺炎（MTX肺炎）

推奨20

① 初期症状に関する患者教育が重要である．MTX開始時には，原因の明らかではない乾性咳嗽，息切れ，呼吸困難感を感じたときは，すみやかに受診をするよう説明する．

② MTX肺炎は投与開始後2～3年以内に発生することが多いが，投与期間の長い症例にも発生する可能性があるので，投与中は常に念頭に置く．開始時および経過中は定期的に胸部画像を評価する．

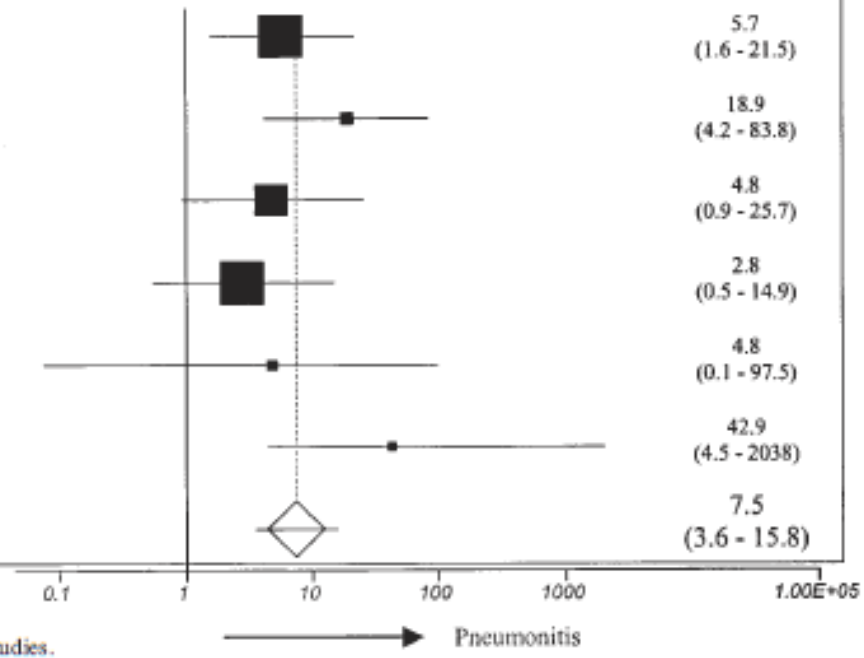
③ MTX肺炎が疑われたときには，すみやかに他の疾患を除外し，中等量～高用量ステロイドを中心とした必要な治療を開始する．

MTX肺炎の発現頻度は報告により異なるが，1～7％前後であるとされる[8,9]．死亡率は13％との報告がある[10]．通常，急性もしくは亜急性の間質性肺炎の経過

MTXは既存IPがあるとMTX肺炎を起こしやすいか？

TABLE 1. A summary of studies on the risk of MTX pneumonitis with pre-existing radiological lung disease

Reference	N	Prior Lung Disease		No Prior Lung Disease	
		Pneumonitis	No Pneumonitis	Pneumonitis	No pneumonitis
Alarcon [9]	111	9	6	20	76
Bartram [10]	1162	5	58	5	1094
Golden [7]	125	5	24	4	92
Carroll [8]	36	7	8	5	16
Howes [6]	120	1	11	2	106
Ohosone [11]	284	5	29	1	249
Pooled Odds Ratio (Random-effects)					



The studies of Alarcon *et al.* [9] and Carroll *et al.* [8] are case-control studies; the others are cohort studies.

β-Dグルカンの日本での保険適応は1995年
FDA認可は2004年 ⇨ やはりPCPが混じっている可能性

Saravanan V Rheumatology 2004; 43: 143

背景2　MTXが動脈硬化疾患の予後を変えるか？

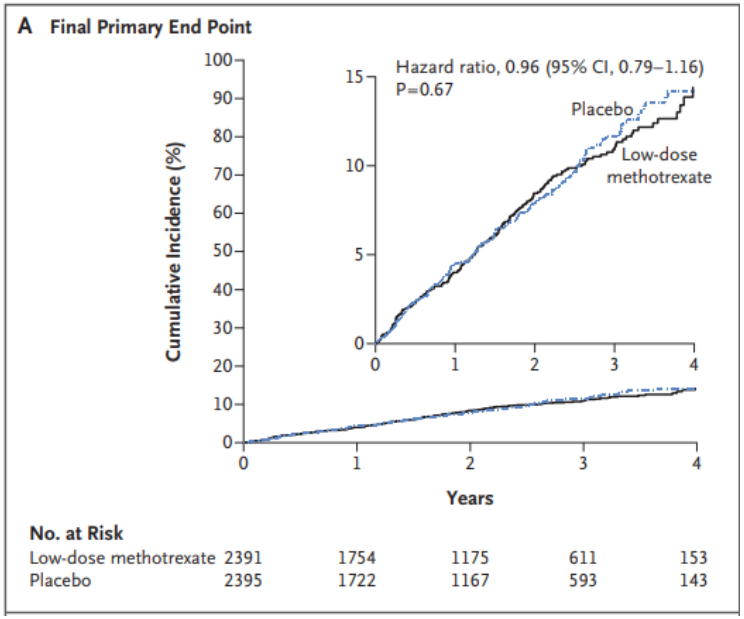
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Low-Dose Methotrexate for the Prevention of Atherosclerotic Events

Paul M Ridker, M.D., Brendan M. Everett, M.D., Aruna Pradhan, M.D., Jean G. MacFadyen, B.A., Daniel H. Solomon, M.D., Elaine Zaharris, B.A., Virak Mam, B.S., Ahmed Hasan, M.D., Yves Rosenberg, M.D., Erin Iturriaga, M.S.N., Milan Gupta, M.D., Michelle Tsigoulis, Subodh Verma, M.D., Michael Clearfield, D.O., Peter Libby, M.D., Samuel Z. Goldhaber, M.D., Roger Seagle, M.D., Cyril Ofori, M.D., Mohammad Saklayen, M.D., Samuel Butman, M.D., Narendra Singh, M.D., Michel Le May, M.D., Olivier Bertrand, M.D., James Johnston, M.D., Nina P. Paynter, Ph.D., and Robert J. Glynn, Sc.D., for the CIRT Investigators*

N Engl J Med 2019;380:752



Annals of Internal Medicine

ORIGINAL RESEARCH

Ann Intern Med. 2020;172:369

Adverse Effects of Low-Dose Methotrexate

A Randomized Trial

Daniel H. Solomon, MD; Robert J. Glynn, PhD; Elizabeth W. Karlson, MD; Fengxin Lu, MD; Cassandra Corrigan, BA; Josh Colls, BA; Chang Xu, MS; Jean MacFadyen, BA; Medha Barbhaiya, MD; Nancy Berliner, MD; Paul F. Dellaripa, MD; Brendan M. Everett, MD; Aruna D. Pradhan, MD; Sarah P. Hammond, MD; Meredith Murray, BA; Deepak A. Rao, MD; Susan Y. Ritter, MD; Anna Rutherford, MD; Jeffrey A. Sparks, MD; Jackie Stratton, BA; Dong H. Suh, BS; Sara K. Tedeschi, MD; Kathleen M.M. Vanni, BA; Nina P. Paynter, PhD*; and Paul M Ridker, MD*

AE	Low-Dose Methotrexate (*n* = 2391)			Placebo (*n* = 2395)		
	Events, *n* (%)†	Rate per 100 Person-Years (95% CI)	3-y Cumulative Incidence (95% CI), %	Events, *n* (%)†	Rate per 100 Person-Years (95% CI)	3-y Cumulative Incidence (95% CI), %
Pneumonitis	7 (0.3)	0.2 (0.0 to 0.3)	0.00 (0.00 to 0.01)	1 (0.0)	0.0 (0.0 to 0.1)	0.00 (0.00 to 0.01)

Clinical Question

P：心血管障害かつ糖尿病/メタボリック症候群の患者

I：MTX (15-20mg/wk)で治療を行う

C：プラセボによる治療（randomized double blind）

O：
1. 主な心血管イベントの発生(MI, 脳卒中, 心臓死）
2. MTXによる重篤な副作用の頻度と差

適格基準

Entry Criteria

1. 心筋梗塞の既往もしくは冠動脈の2 or 3枝病変をもつ

2. 糖尿病　または　メタボリックシンドロームを合併

など

Exclusion Criteria

1. 全身性リウマチ性疾患、慢性肝障害、慢性感染症、間質性肺炎

2. NYHA class IV 心不全

など

介入

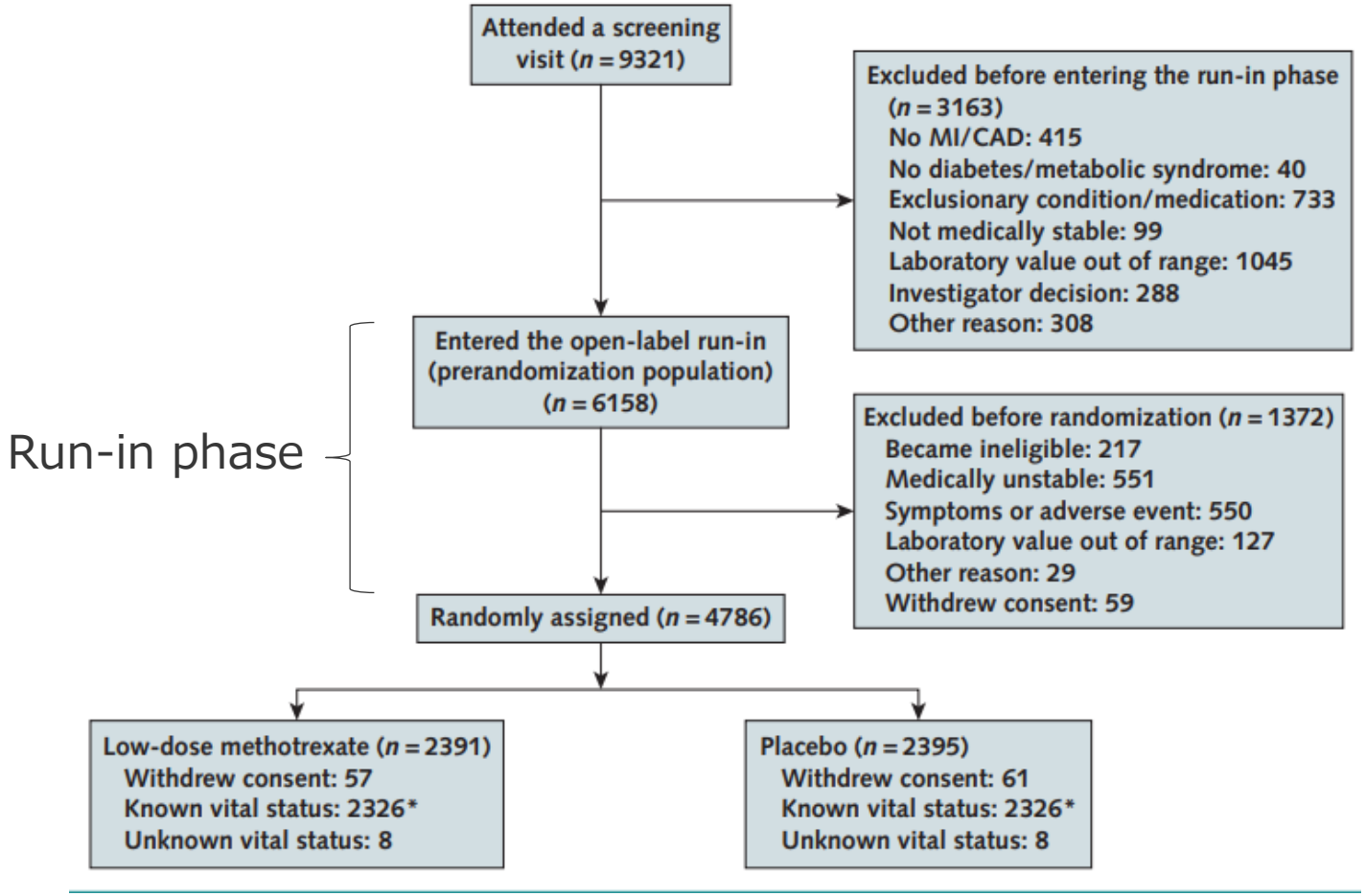
ランダム割付前のrun-in phase（慣らし運転期間）

MTX 10-15mg/wk + 葉酸 1mg/day（他の6日間）を5－８週間行い、内服可能な患者のみがランダム割り付けされる。

ランダム割付

MTX or placebo に1:1に割り付け。Double blind。

Study Design



1. **MTX群**：MTX 15mg/wkで開始し、16週後に安全性が確認できたら20mg/wkに増量する。葉酸を1mg/day 週６日間内服。

2. **Placebo群**：Placebo を週１回内服、葉酸を1mg/day 週６日間内服。

アウトカム

1. 主な心血管イベントの発生(MI, 脳卒中, 心臓死）　NEJM
2. MTXによる重篤な副作用の頻度と差　AIM
3. MTXによる肺障害の詳細とその予測因子　A&R

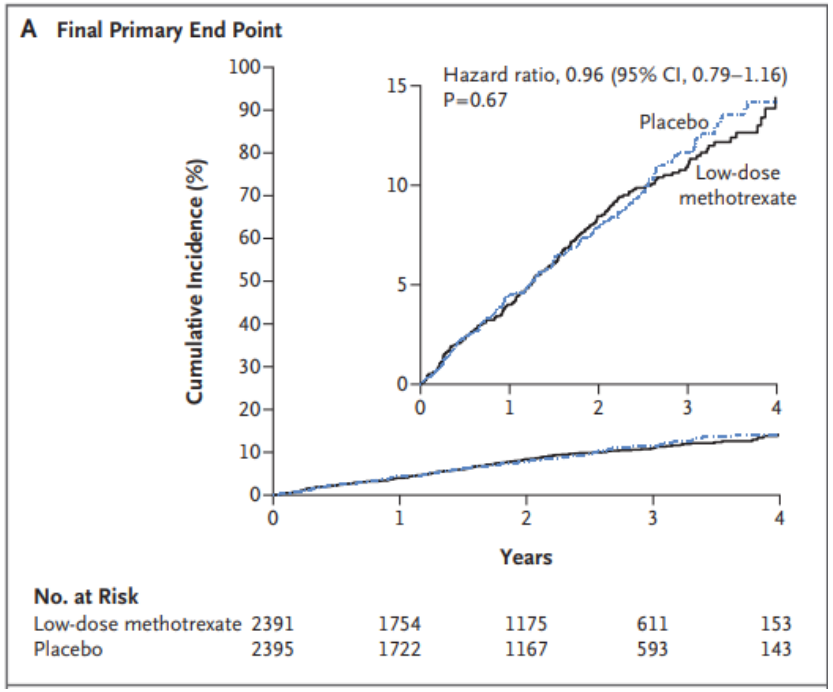


Table 5. Frequency and Relative Risks Comparing Infection and Pulmonary AEs for Methotrexate Versus Placebo During the Randomized Phase of CIRT*

AE	Low-Dose Methotrexate (*n* = 2391)			Placebo (*n* = 2395)			Risk Difference (95% CI)‡	Hazard Ratio (95% CI)
	Events, *n* (%)†	Rate per 100 Person-Years (95% CI)	3-y Cumulative Incidence (95% CI), %	Events, *n* (%)†	Rate per 100 Person-Years (95% CI)	3-y Cumulative Incidence (95% CI), %		
Infection								
Any	531 (22.2)	13.6 (12.4 to 14.8)	0.31 (0.28 to 0.34)	466 (19.5)	11.8 (10.8 to 12.9)	0.27 (0.25 to 0.30)	0.04 (0.00 to 0.07)	1.15 (1.01 to 1.30)
Mild	340 (14.2)	8.2 (7.4 to 9.1)	0.20 (0.18 to 0.23)	282 (11.8)	6.8 (6.0 to 7.6)	0.16 (0.14 to 0.18)	0.04 (0.01 to 0.07)	1.21 (1.03 to 1.42)
Moderate	241 (10.1)	5.6 (4.9 to 6.3)	0.14 (0.12 to 0.16)	219 (9.1)	5.1 (4.4 to 5.7)	0.13 (0.12 to 0.16)	0.01 (−0.02 to 0.03)	1.10 (0.91 to 1.32)
Severe	51 (2.1)	1.1 (0.8 to 1.4)	0.03 (0.02 to 0.04)	50 (2.1)	1.1 (0.8 to 1.4)	0.03 (0.03 to 0.05)	0.00 (−0.02 to 0.01)	1.02 (0.69 to 1.50)
By type								
Upper respiratory infection/flu syndrome	125 (5.2)	2.8 (2.3 to 3.3)	0.08 (0.07 to 0.10)	105 (4.4)	2.4 (1.9 to 2.8)	0.06 (0.05 to 0.08)	0.01 (0.00 to 0.03)	1.19 (0.92 to 1.54)
Skin and soft tissue	129 (5.4)	2.9 (2.4 to 3.4)	0.08 (0.07 to 0.09)	125 (5.2)	2.8 (2.3 to 3.3)	0.08 (0.07 to 0.10)	0.00 (−0.02 to 0.02)	1.03 (0.80 to 1.31)
Pneumonia	67 (2.8)	1.5 (1.1 to 1.8)	0.04 (0.03 to 0.06)	52 (2.2)	1.1 (0.8 to 1.4)	0.03 (0.02 to 0.04)	0.01 (0.00 to 0.02)	1.28 (0.89 to 1.83)
Eye, ear, nose, throat, and dental	182 (7.6)	4.1 (3.5 to 4.7)	0.11 (0.09 to 0.13)	149 (6.2)	3.4 (2.9 to 4.0)	0.08 (0.07 to 0.10)	0.03 (0.01 to 0.05)	1.21 (0.98 to 1.51)
Genitourinary	111 (4.6)	2.5 (2.0 to 2.9)	0.06 (0.05 to 0.08)	86 (3.6)	1.9 (1.5 to 2.3)	0.05 (0.04 to 0.07)	0.01 (−0.01 to 0.03)	1.30 (0.98 to 1.72)
Gastrointestinal	37 (1.5)	0.8 (0.5 to 1.1)	0.02 (0.02 to 0.03)	35 (1.5)	0.8 (0.5 to 1.0)	0.02 (0.02 to 0.03)	0.00 (−0.01 to 0.01)	1.05 (0.66 to 1.67)
Shingles	23 (1.0)	0.5 (0.3 to 0.7)	0.01 (0.01 to 0.02)	17 (0.7)	0.4 (0.2 to 0.5)	0.01 (0.01 to 0.02)	0.00 (0.00 to 0.01)	1.34 (0.72 to 2.51)
Bone and joint	21 (0.9)	0.5 (0.3 to 0.6)	0.01 (0.01 to 0.02)	11 (0.5)	0.2 (0.1 to 0.4)	0.01 (0.01 to 0.02)	0.00 (0.00 to 0.01)	1.91 (0.92 to 3.96)
Yeast	6 (0.3)	0.1 (0.0 to 0.2)	0.00 (0.00 to 0.01)	9 (0.4)	0.2 (0.1 to 0.3)	0.01 (0.00 to 0.01)	0.00 (0.00 to 0.00)	0.66 (0.24 to 1.83)
Sepsis	12 (0.5)	0.3 (0.1 to 0.4)	0.01 (0.00 to 0.01)	14 (0.6)	0.3 (0.1 to 0.5)	0.01 (0.00 to 0.01)	0.00 (−0.01 to 0.00)	0.85 (0.39 to 1.82)
Not otherwise specified	22 (0.9)	0.5 (0.3 to 0.7)	0.01 (0.01 to 0.03)	22 (0.9)	0.5 (0.3 to 0.7)	0.01 (0.01 to 0.02)	0.00 (−0.01 to 0.01)	0.99 (0.55 to 1.79)
Pulmonary events								
Any	137 (5.7)	3.1 (2.6 to 3.6)	0.08 (0.07 to 0.10)	135 (5.6)	3.1 (2.5 to 3.6)	0.06 (0.05 to 0.07)	0.03 (0.01 to 0.04)	1.42 (1.14 to 1.77)
Mild	77 (3.2)	1.7 (1.3 to 2.1)	0.05 (0.04 to 0.06)	66 (2.8)	1.5 (1.1 to 1.8)	0.03 (0.02 to 0.05)	0.01 (0.00 to 0.03)	1.40 (1.02 to 1.93)
Moderate	50 (2.1)	1.1 (0.8 to 1.4)	0.03 (0.02 to 0.04)	61 (2.5)	1.3 (1.0 to 1.7)	0.02 (0.01 to 0.03)	0.01 (0.00 to 0.02)	1.41 (1.02 to 1.96)
Severe	13 (0.5)	0.3 (0.1 to 0.4)	0.01 (0.00 to 0.02)	8 (0.3)	0.2 (0.1 to 0.3)	0.00 (0.00 to 0.00)	0.01 (0.00 to 0.01)	2.99 (1.34 to 6.65)
By type								
Bronchitis	116 (4.9)	2.6 (2.1 to 3.1)	0.07 (0.06 to 0.08)	73 (3.0)	1.6 (1.3 to 2.0)	0.04 (0.03 to 0.06)	0.02 (0.01 to 0.04)	1.60 (1.19 to 2.14)
Cough	4 (0.2)	0.1 (0.0 to 0.2)	0.00 (0.00 to 0.01)	5 (0.2)	0.1 (0.0 to 0.2)	0.00 (0.00 to 0.01)	0.00 (0.00 to 0.00)	0.80 (0.21 to 2.96)
Shortness of breath	11 (0.5)	0.2 (0.1 to 0.4)	0.04 (0.03 to 0.06)	8 (0.3)	0.2 (0.1 to 0.3)	0.03 (0.02 to 0.04)	0.01 (0.00 to 0.02)	1.36 (0.55 to 3.38)
COPD/asthma flare	3 (0.1)	0.1 (0.0 to 0.1)	0.01 (0.00 to 0.01)	6 (0.3)	0.1 (0.0 to 0.2)	0.01 (0.00 to 0.02)	0.00 (−0.01 to 0.00)	0.50 (0.13 to 1.99)
Pneumonitis	7 (0.3)	0.2 (0.0 to 0.3)	0.00 (0.00 to 0.01)	1 (0.0)	0.0 (0.0 to 0.1)	0.00 (0.00 to 0.01)	0.00 (0.00 to 0.00)	6.94 (0.85 to 56.6)
Not otherwise specified	1 (0.0)	0.0 (0.0 to 0.1)	0.00 (0.00 to 0.01)	2 (0.1)	0.0 (0.0 to 0.1)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.01)	0.48 (0.04 to 5.37)

AE = adverse event; CIRT = Cardiovascular Inflammation Reduction Trial; COPD = chronic obstructive pulmonary disease.
* Based on the modified intention-to-treat analyses (see text for details).
† Includes first events of a given type; percentages refer to the number of participants with a given AE divided by all participants in the respective treatment group. The first mild, moderate, and severe event, as well as the first of each type of AE, were included.
‡ Based on the 3-y cumulative incidence percentage of risk.

ここから本研究

P：心血管障害かつ糖尿病/メタボリック症候群の患者

I：MTX (15-20mg/wk)で治療を行う

C：プラセボによる治療（randomized double blind）

O：MTXによる重篤な肺障害の記述とその予測因子

解析

- 肺障害はblindのまま評価者にて肺障害のclassificationを行う。間質性肺炎の評価は症状、データ、画像を総合して行った。
- MTX関連肺障害と関連するランダム化時点での因子をCox回帰モデルにて解析
- 多変量解析ではp<0.2となるすべての因子にて解析

間質性肺炎（possible pneumonitis)をきたした患者8例の詳細（MTX群7例、プラセボ群1例）

Table 1. Cases of possible pneumonitis events (n = 8) among subjects randomized to receive low-dose MTX or placebo in the CIRT (n = 4,786)*

Case no.	Age at baseline, years	Sex	Ever smoker	Months from randomization to clinical onset	Weekly study drug dose at clinical presentation	Case narrative	Vital status
Randomized to receive low-dose MTX							
1	68	Male	No	15	20 mg	Dry cough started after study drug initiation with progressive mild dyspnea. PFTs showed restrictive pattern. Chest CT scan showed peripheral reticulation with lower lung predominance consistent with usual interstitial pneumonia or fibrotic nonspecific interstitial pneumonia. Symptoms improved after discontinuing study drug.	Alive
2	67	Male	No	15	20 mg	Developed subacute, progressive onset of dyspnea and was hospitalized for hypoxemia when study drug was discontinued. Chest CT scan showed bilateral nodular infiltrates. Treated for possible pneumonia and volume overload without improvement. Pathology from lung biopsy was consistent with interstitial lung disease.	Alive
3	68	Male	No	4	0 mg†	Acute on chronic worsening dyspnea; chest CT scan showed pulmonary fibrosis. Study drug and amiodarone were discontinued, and prednisone was started. Pathology from lung biopsy showed pulmonary fibrosis. Dyspnea progressed, and patient died of respiratory failure while in hospice care. Autopsy showed interstitial lung disease with usual interstitial pneumonia pattern and diffuse alveolar damage.	Died
4	70	Male	No	27	20 mg	Increased intermittent dyspnea prompted chest CT scan that showed possible mild pulmonary fibrosis; study drug was discontinued.	Alive
5	79	Male	No	24	20 mg	Hospitalized for gradually progressive dyspnea. Chest CT scan showed bibasilar honeycombing and pulmonary fibrosis. Study drug was discontinued, and prednisone was started. Unclear clinical course, but death certificate listed chronic interstitial pneumonia and pulmonary fibrosis as cause of death.	Died
6	77	Male	No	2	15 mg	Developed worsening dyspnea on exertion; chest CT scan showed extensive bilateral reticulonodular interstitial opacities and study drug was discontinued. PFTs with mild restriction and diffusion abnormality. Imaging and symptoms remained stable during follow-up.	Alive
7	65	Male	No	17	0 mg†	Developed new cough and infiltrates were detected on chest plain radiograph, so study drug was discontinued. Chest CT scan showed mediastinal and subcarinal lymphadenopathy and reticular pattern ground-glass opacities. PFTs showed a restrictive pattern. Whole-body positron emission tomography showed mild FDG-avidity of lymph nodes. Clinically thought to be due to either sarcoidosis or study drug use.	Alive
Randomized to receive placebo							
1	73	Male	Yes	11	20 mg	Developed new-onset shortness of breath, and ground-glass opacities were detected on chest radiograph and chest CT scan. Antibiotics were started for possible pneumonia. Amiodarone and study drug were discontinued. Symptoms and imaging abnormalities resolved during follow-up.	Alive

* MTX = methotrexate; CIRT = Cardiovascular Inflammation Reduction Trial; PFTs = pulmonary function tests; CT = computed tomography; FDG = fluorodeoxyglucose.
† These subjects had discontinued study drug due to pulmonary symptoms prior to clinical presentation.

MTXによる肺障害の予測因子

Table 2. Baseline predictors of initial pulmonary adverse event (any level of severity) (n = 137) among subjects randomized to receive low-dose MTX in the CIRT (n = 2,391)*

Baseline variable	Unadjusted HR (95% CI)	Multivariable HR (95% CI)
Age, per year	1.01 (0.99–1.03)	–
Age, binary		
<60 years	1.00 (referent)	1.00 (referent)
≥60 years	1.06 (0.73–1.55)	0.99 (0.68–1.44)
Female sex (versus male)	1.71 (1.18–2.48)†	1.69 (1.16–2.45)†
Race		
African American	1.00 (referent)	1.00 (referent)
White	1.89 (0.84–4.30)	2.35 (1.03–5.36)†
Asian	0.32 (0.04–2.65)	0.42 (0.05–3.49)
Other	0.92 (0.23–3.68)	1.10 (0.27–4.39)
Body mass index category		
Normal or underweight (<25 kg/m^2)	1.00 (referent)	–
Overweight (25 to <30 kg/m^2)	1.85 (0.78–4.37)	–
Obese (≥30 kg/m^2)	2.04 (0.89–4.66)	–
Diabetes mellitus	1.18 (0.82–1.70)	–
Insulin use	1.76 (1.22–2.52)†	1.60 (1.11–2.30)†
Metabolic syndrome	0.96 (0.67–1.38)	–
Respiratory medication use‡	3.96 (2.76–5.68)†	2.78 (0.39–19.99)
Alcohol intake, per drink/week	0.98 (0.79–1.23)	–
Ever smoked (versus never smoked)	1.34 (0.82–2.17)	–
Oral corticosteroids	1.27 (0.31–5.11)	–
Inhaled corticosteroids	3.99 (2.78–5.74)†	1.39 (0.19–10.14)
Albumin <3.9 gm/dl (versus ≥3.9)§	1.14 (0.42–3.09)	–

* MTX = methotrexate; CIRT = Cardiovascular Inflammation Reduction Trial; HR = hazard ratio; 95% CI = 95% confidence interval.
† Significantly associated with an increased risk of any pulmonary adverse event.
‡ Respiratory medications included nonsteroid, steroid, and combination inhalers as well as oral or subcutaneous medications approved for use in asthma or chronic obstructive pulmonary disease.
§ Data were missing for 6 patients.

MTXによる重篤な肺障害の予測因子

Table 3. Baseline predictors of initial severe pulmonary adverse event (n = 13 outcomes) among subjects randomized to receive low-dose MTX in the CIRT (n = 2,391)*

Baseline variable	Unadjusted HR (95% CI)
Age, per year	1.09 (1.02–1.16)†
Age, binary	
<60 years	1.00 (referent)
≥60 years	4.67 (0.61–35.97)
Male sex (versus female)	0.36 (0.17–3.45)
Race	
White	1.00 (referent)
African American	–‡
Asian	–‡
Other	1.78 (0.23–13.65)
Diabetes mellitus	0.80 (0.26–2.44)
Insulin use	1.66 (0.51–5.39)
Metabolic syndrome	0.53 (0.18–1.59)
Respiratory medication use§	2.43 (0.67–8.81)
Alcohol intake, per drink/week	1.58 (0.83–2.98)
Ever smoked (versus never smoked)	0.67 (0.09–5.18)
Inhaled corticosteroids	2.53 (0.70–9.21)
Albumin <3.9 gm/dl (versus ≥3.9 gm/dl)¶	0.41 (0.05–3.13)

* MTX = methotrexate; CIRT = Cardiovascular Inflammation Reduction Trial; HR = hazard ratio; 95% CI = 95% confidence interval.
† Significantly associated with an increased risk of any pulmonary adverse event.
‡ No events occurred in these strata.
§ Respiratory medications included nonsteroid, steroid, and combination inhalers as well as oral or subcutaneous medications approved for use in asthma or chronic obstructive pulmonary disease.
¶ Data were missing for 6 patients.

結論

MTXによる間質性肺炎の頻度は0.3%程度

そのリスク因子は年齢のみ

Limitation:

1. 投与前にCTを撮影していないので、
   肺病変の有無はX-Pのみでの判断
2. MTX投与可能だったひとのみをf/uして
   いるため、過小評価の可能性