厚生労働科学研究費補助金（免疫アレルギー疾患等予防・治療研究事業）
研究分担報告書

SAKURA 早期関節炎コホートにおける高感度サイトカインアッセイ系による検討

研究分担者　　竹内　勤　　慶應義塾大学医学部リウマチ内科　教授

研究要旨

日常診療下の早期 RA に対するメトトレキサート投与例における、血中サイトカイン変動を、Electro-chemiluminescence (ECL)による超感度アッセイ系により解析した。

平均罹病期間 0.6 年の早期 RA コホート62例においてIL-1βとIL-6 の有意な低下を明らかにした。その中で、関節破壊進行と関連する治療後サイトカインを検討した所、治療後 TNFαは抽出されず、従来型 ELISA 法と同様 IL-6 が有用なバイオマーカーである事が示された。

A.研究目的

日常診療下の早期 RA に対するメトトレキサート投与例における、血中サイトカイン変動を、Electro-chemiluminescence (ECL)による超感度アッセイ系により解析する。

B.研究方法

1.対象患者：慶應義塾大学リウマチ内科で、2008年8月から前向きに登録された新規診断 RA コホート SAKURA の中から、第一 DMARD として MTX が投与された 62 例を対象とした。2.臨床データ：62例の MTX 投与前、MTX 投与1年後の DAS28-ESR, SDAI, CDAI, CRP, MMP-3 などのの臨床パラメーターを収集した。3.血漿サイトカイン：MSD 社のルテニウム標識抗体による ultra-sensitive ELISA 9-plex キット（ECL 法）を用いて、MTX 投与前と投与1年後の患者血漿サイトカイン（IL-1β, IL-2, IL-6, IL-8, IL-10, TNFα, IFNγ, GM-CSF, を測定した。4.手足 X-P のスコアリング：van der heijde modified sharp　法によって、62例の MTX 投与前後の写真を2名の読影者（K.Y., N.N.）がスコアー化 (mTSS)した。5.統計解析：JMP9.0 ソフトウエアーを用いて統計解析した。

（倫理面への配慮）

2011 年 12 月 26 日付で、慶應義塾大学医学部倫理委員会にて同研究内容は、多施設共同研究として承認されている(No.2011-231)。

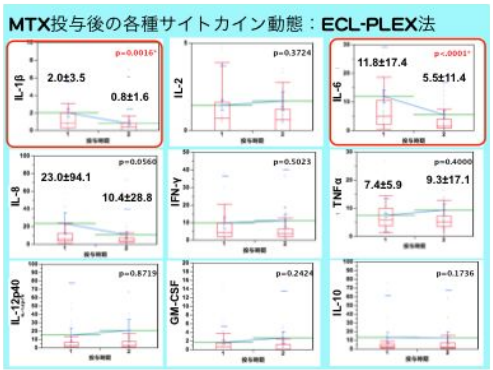
C.研究結果

1）患者背景と臨床効果：昨年報告した通り、女性 79%、年齢 56±14.5 才、罹病期間　6.3±8.0 ヶ月、RF+ 74.2%、抗 CCP 74.2%、MTX 用量 8.7±2.3mg/週。MTX 投与前の DAS28-ESR　高疾患活動性 33.9%、中疾患活動性 56.5%、低疾患活動性 6.5%、寛解 3.2%、MTX 投与1年後の DAS28-ESR　高疾患活動性 1.6%、中疾患活動性 22.6%、低疾患活動性 25.8%、寛解 50.0%、と、半数が臨床的寛解を達成、3／4が低疾患活動性以上を達成した。

2）IL-6 と TNFαの従来型 ELISA 法と超高感度 ECL 法の比較：MTX 投与前後の IL-6 と、TNFαに関して、両アッセイ系によって比較した。IL-6 の両アッセイの相関は、r=0.864, p<0.0001 と良好で、TNFαは、r=0.659, p<0.001 と IL-6 に比較し相関が低かった。IL-6 は、従来型 ELISA 法で 20.9±47.3pg/ml で検出限界に近い 1pg/ml 以下を9例（14.5%）に、検出不能例を2例に認めた。一方、超高感

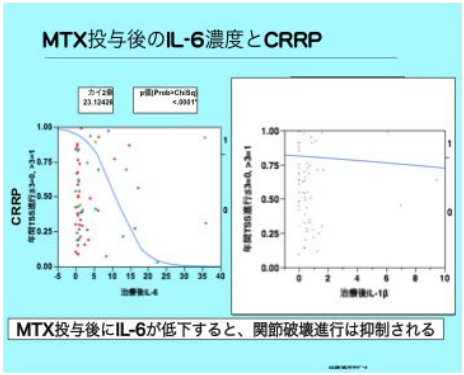
度 ECL 法による IL-6 は 11.8±17.4 pg/ml で、1pg/ml 以下は4例 (6.5%) であったが、検出不能例は認めなかった。TNF α は、従来型 ELISA 法で 1.0±1.3pg/ml で検出限界に近い 1pg/ml 以下を33例 (53.2%) に、検出不能例を26例 (41.9%) に認めた。一方、超高感度 ECL 法による TNF α は 7.0±4.6 pg/ml で、1pg/ml 以下は0例、検出不能例を認めなかった。いずれのサイトカインにおいても ultra-sensitive ECL アッセイ系の優越性が明らかとなった。特に、TNF α 測定においては、超高感度 ECL アッセイ法は、検出不能例がなく、優れた検出系と考えられた。

[図1]



3) 治療後サイトカインの変動 (図1) : 治療前後で有意に変化したサイトカインは、IL-1βとIL-6であった。IL-1βは治療前2.0±3.5 pg/mlから、治療後0.8±1.6 pg/mlへと低下した (p=0.0016)。IL-6は、治療前11.8±17.4 pg/mlから治療後5.5±11.4 pg/mlへと68%低下した (p<0.0001)。一方、TNF α は、超高感度ECL法によっても、治療前7.0±4.6 pg/mlから治療後9.3±17.1 pg/ml(p=0.400)と変化無く、IL-2, IL-8, IL-10, IFNγ, GM-CSFも有意な変化を示さなかった。

4) CRRPと関連するMTX投与1年後の要因: ΔTSS>3以上のclinically relevant radiographic progression (CRRP)と関連する治療後サイトカインを解析した所、ロジスティック回帰分析によって、唯一治療後IL-6がCCRPと関連する要因として抽出された (単位オッズ比＝1.92、95%信頼区間＝1.30-3.63)。CRRPを来すIL-6値をROC解析によって求めた所、2.4pg/mlのカットオフが得られた (図2)。一方、高感度ECL法によっても、治療後TNF α の単位オッズ比は1.08、95%信頼区間は0.50-1.91であった。



D. E.考察/結論

平均罹病期間 0.6 年の早期 RA コホート62例で MTX の関節破壊抑制効果と血中サイトカイン9種類の変動を超高感度 ECL 法で解析し、IL-1βと IL-6 の有意な低下を明らかにした。その中で、関節破壊進行と関連する治療後サイトカインを検討した所、治療後 TNF α は抽出されず、従来型 ELISA 法と同様 IL-6 が有用なバイオマーカーである事が示された。

F.健康危険情報

特記すべきことなし。

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H.知的財産権の出願・登録状況（予定も含む）

1. 特許取得

特になし

2. 実用新案登録

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3. その他

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