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難治性疾患等克服研究事業（免疫アレルギー疾患等予防・治療研究事業）
分担研究報告書

早期 RA に対する MTX の関節破壊抑制効果に関する解析

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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の関節破壊抑制効果に着目し、それと関連する臨床的要因、サイトカイン変動を、慶應義塾大学リウマチ内科の早期 RA コホートで解析した。関節リウマチ治療薬のアンカードラッグであるメトトレキサートを日常臨床で経験する中疾患活動性の症例に投与した場合、76%が最低限の治療目標である低疾患活動性を1年後に満足するが、その時の構造的寛解は65%に留まり、一方、32%が臨床的に問題となる関節破壊進行(CRRP)を示し、18%が急速に関節破壊進行を来す事が SAKURA コホートの解析から明らかとなった。関節破壊進行と関連する血漿サイトカインとして 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 に対するメットレキサートの関節破壊抑制効果に着目し、それと関連する臨床的要因、サイトカイン変動を、慶應義塾大学リウマチ内科の早期 RA コホートから解析する。

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

臨床パラメーターを収集した。1年以内に MTX 単独治療が終了した症例では、その最終単独等予備の臨床データを LOCF して解析した。

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)。

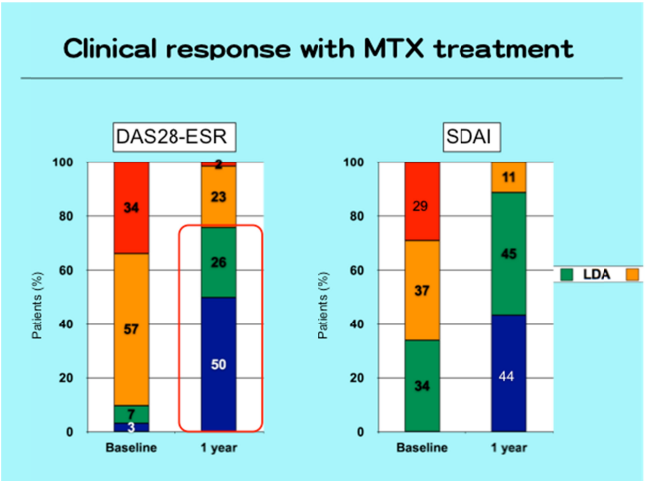
C.研究結果

1）患者背景：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。

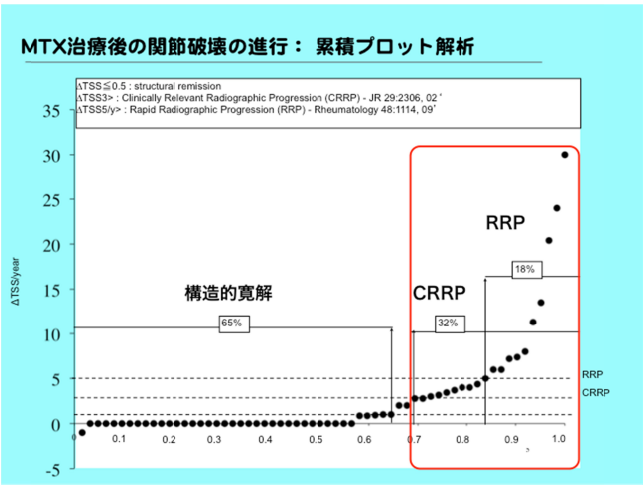
2）臨床効果（図1）：MTX 投与前の DAS28-ESR 高疾患活動性 33.9%、中疾患活動性 56.5%、低疾患活動性 6.5%、寛解 3.2%、MTX 投与1年後の DAS28-ESR 高疾患活動性 1.6%、中疾患活動性 22.6%、

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。3）関

節破壊の進行：MTX 投与前の mTSS 8.7+/-20.3、MTX 投与1年後の mTSS 11.1+/-21.1。



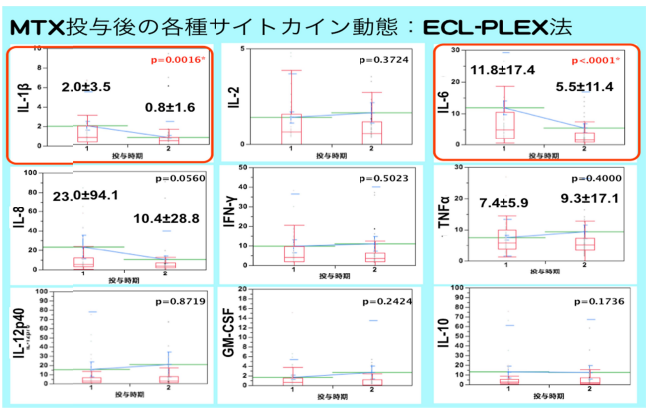
4）構造的寛解とCRRP/RRP（図2）：構造的寛解は65%、Clinically relevant radiographic progression (CRRP) 32%、Rapid radiographic progression (RRP) 18%。



5）血漿IL-6濃度はMTX投与前4.72pg/mlから1.04pg/mlへと78%低下したのに対し、TNFaは0.87pg/mlから-0.83pg/mlと有意な低下を認めなかった。

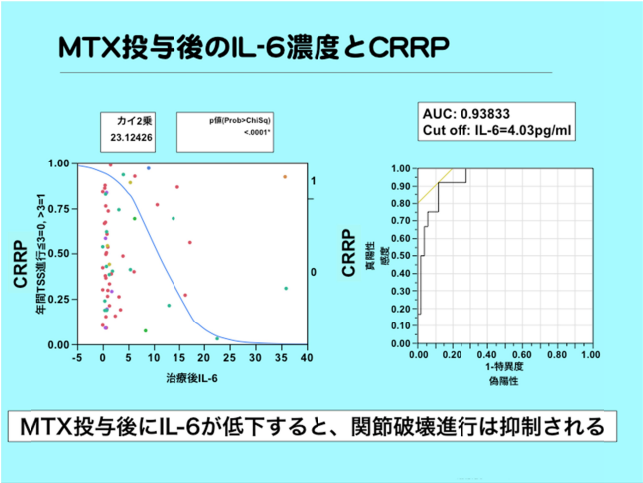
6）IL-6とTNFαの従来型ELISA法と超高感度ECL法の比較：MTX投与前後のIL-6と、TNFαに関して、両アッセイ系によって比較した。IL-6の両アッセイの相関は、r=0.864, p<0.0001と良好で、TNFαは、r=0.659, p<0.001とIL-6に比較し相関が低かった。IL-6は、従来型ELISA法で20.9±47.3pg/mlで検出限界に近い1pg/ml以下を9例（14.5%）に、検出不能例を2例に認めた。一方、超高感度ECL法によるIL-6は11.8±17.4 pg/mlで、1pg/ml以下は4例（6.5%）であったが、検出不能例は認めなかった。TNFαは、従来型ELISA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TNFα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、TNFα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。

7）3）治療後サイトカインの変動（図3）：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、TNFα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。



8）年間関節破壊進行度と関連するMTX投与1年後の要因：クラスター解析によってestimated yearly progressionとの相関を解析した所、これとクラスターを形成する要因として、MTX投与1年後のIL-6値、MMP-3の二つが明らかとなった。最も相関が強かったMTX投与後IL-6値と臨床的に問題となる関節破壊進行CRRPの関連をロジスティック回帰分析した所、この両者はp<0.0001で有意に関連し、

CRRP を来す IL-6 値を ROC 解析によって求めた所、4pg/ml のカットオフが AUC=0.938、感度 91%、特異度 89%の優れた数値を示す事が明らかとなった。(図4)



D.考察/E.結論

関節リウマチ治療薬のアンカードラッグであるメトトレキサートを日常臨床で経験する中疾患活動性の症例に投与した場合、76%が最低限の治療目標である低疾患活動性を1年後に満足するが、その時の構造的寛解は65%に留まり、一方、32%が臨床的に問題となる関節破壊進行(CRRP)を示し、18%が急速に関節破壊進行を来す事がSAKURA コホートの解析から明らかとなった。関節破壊進行と関連する血漿サイトカインとして 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

G.研究発表

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H.知的財産権の出願・登録状況

（予定を含む）

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし