

# 厚生労働科学研究費補助金 難治性疾患克服研究事業

骨髄幹細胞移植による難治性血管炎への血管再生医療に  
関する多施設共同研究

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# 綜合研究報告

厚生労働省科学研究費補助金（難治性疾患克服研究事業）  
研究報告書

「骨髄幹細胞移植による難治性血管炎への血管再生医療に関する  
多施設共同研究」

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研究要旨：

難治性血管炎患者に対する自己骨髄細胞移植による血管再生療法の有効性と安全性を多施設臨床試験により検証し、さらに、疾患モデル動物を用いた基礎的研究により本治療法の作用機序を解明して、より侵襲が少ない治療法を開発することを目的として本研究を行った。班員施設で計126例の重症虚血指趾患者（ASO 76例、バージャー病40例、膠原病14例）に本治療法を施行した。バージャー病での有効率は96.3%であり、膠原病での有効率は71.4%であった。特に、膠原病の中でも、SScでは全例で皮膚潰瘍や疼痛などの症状の著明な改善を認めた。また、多施設臨床試験（TACT）の追跡調査によりバージャー病ではASOに比較して有効性が高く、治療効果も持続することが明らかとなった。さらに、基礎的研究では、薬剤やサイトカインの投与により骨髄採取による患者負担を減少させて効果的な血管新生や血管修復作用を誘導する可能性が示された。

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で明らかとしてきた。しかし、より多くのバージャー病症例での検証が必要であり、膠原病性の難治性血管炎における本治療法の有効性についても未だ明らかではない。そこで、本研究では、臨床試験により難治性血管炎患者に対する自己骨髄細胞移植による血管再生療法の有効性と安全性を検証することを目的として研究を行った。また、その作用機序の解明や全身麻酔下での骨髄採取を必要としないより侵襲の少ない新たな血管再生療法の開発も重要な課題であることから、基礎的研究による作用機序の解明とより侵襲の少ない新たな治療法の開発についても目的としている。

A. 研究目的

難治性血管炎は、特定疾患の一つに指定されており、特定従来の治療法が無効で指趾切断に至る症例も少なくない。申請者らは、骨髄細胞移植療法が閉塞性動脈硬化症（ASO）やバージャー病による重症虚血肢に有効であることをす

B. 研究方法

(1) 多施設臨床試験による骨髄幹細胞移植療法の有効性と安全性の検証  
平成16年度から全国5施設で研究班を組織し

本研究を開始した。その後、膠原病での血管再生療法を行った症例数が少ないことから、平成18年度から4施設を加えて多施設臨床試験を行った。班施設で計126例の重症虚血指趾患者（ASO 76例、バージャー病40例、膠原病14例〔強皮症（SSc）9例、CREST症候群2例、混合性結合組織病（MCTD）1例、結節性多発性動脈炎（PN）1例、抗リン脂質症候群（APS）1例〕、その他7例に自己骨髄細胞移植療法を施行した。また、TACT臨床試験におけるASOとバージャー病の本治療法の治療後2年および4年までの臨床成績を集計してそれらの臨床経過や長期予後、有害事象についての解析を行った。評価項目としては、疼痛レベル（VAS）や上下肢血圧比（ABI）、潰瘍直径、歩行距離などについて検討した。

(2) 基礎的研究による作用機序の解明とより侵襲の少ない新たな治療法の開発

マウス下肢虚血および血管傷害モデルを作製して、顆粒球コロニー刺激因子（G-CSF）やエリスロポエチン（EPO）、マクロファージコロニー刺激因子（M-CSF）の作用を検討した。さらに、アンジオポエチン-1（Ang-1）やEPOの骨髄幹細胞移植との併用による効果についても検討を行った。骨髄幹細胞動員効果についてはフローサイトメトリー法で、治療効果についてはレーザードップラーによる血流評価や組織学的解析により検討した。

（倫理面への配慮）

本臨床研究は、すでに各研究者所属機関における倫理委員会の承認を得ている。本臨床研究に参加する患者には、十分な説明と同意によりインフォームドコンセントを得る。患者データの解析については、患者番号による匿名化を行う。ヒト組織・細胞を研究に用いる場合は、「手術等で摘出されたヒト組織を用いた研究開発の在り方について」（平成10年度厚生科学審議会答申）ならびに各研究者所属機関における倫理委員会規定に基づき、同委員会の承諾と十分なインフォームドコンセントのもとに行う。また、動物実験については、各研究者所属機関における委員会規定に基づき、同委員会の

承諾と十分な配慮のもとで実施する。

## C. 研究結果

(1) 多施設臨床試験による骨髄幹細胞移植療法の有効性と安全性の検証

班員施設で計126例の重症虚血指趾患者（ASO 76例、バージャー病40例、膠原病14例〔強皮症（SSc）9例、CREST症候群2例、混合性結合組織病（MCTD）1例、結節性多発性動脈炎（PN）1例、抗リン脂質症候群（APS）1例〕、その他7例に自己骨髄細胞移植療法を施行した。このうち、バージャー病40例での有効率は96.3%であり、膠原病での有効率は71.4%であった。膠原病の中でも、強皮症では治療経過の違いはあるが、全例で皮膚潰瘍や疼痛などの症状の著明な改善を認めた。他の膠原病関連血管炎症例では非改善例が多く、今後の症例の積み重ねが重要であると考えられる。また、TACT臨床試験の2年後までの追跡調査（平成17年3月）により、ASOおよびバージャー病における本治療後の予後としては、疼痛スケール（VAS）、上下肢血圧比（ABI）、潰瘍サイズ、歩行距離などの指標は、移植後に有意に改善していたが、その改善度はASOでは経過と共に低下する傾向にあるが、バージャー病では治療効果が長期持続する傾向にあることを明らかとした。有害事象については、バージャー病で3例（4.6%：心筋梗塞、膵炎、胃癌が各1例）、ASOで11例（8.8%）を認めた。さらに、TACT臨床試験の4年後までの追跡調査（平成19年3月日本循環器学会総会〔神戸〕にて発表）で計115例の重症虚血指趾（ASO 74例、バージャー病41例）を解析した。3年目の生存率は、ASOで80%、バージャー病で100%であり指趾の切断率はASOで53%、バージャー病で94%であった。ASOでの死亡は敗血症3例、心不全2例を含む11例であり、有害事象については、バージャー病で1例（動脈血栓）、ASOで15例（急性冠症候群1例、心不全1例、狭心症1例、脳卒中3例、重症感染症4例など）を認めた。これらのことから、バージャー病ではASOに比較して有効性が高く、治療効果も持続するこ

とが明らかとなった。

## (2) 基礎的研究による作用機序の解明とより侵襲の少ない新たな治療法の開発

より侵襲の少ない治療法として、G-CSFやEPOの投与が骨髄幹細胞を末梢血中に動員して血管新生作用および傷害血管への修復作用を示すことを報告した。また、臨床的にG-CSFによる血栓などの副作用が報告されていることから、低用量G-CSFの虚血部位局所への直接作用を検討し、低用量 G-CSF の局所投与によって虚血部位での血管新生が誘導され、血流が改善することが示された。一方、単球系細胞の動員を誘導する M-CSF は、傷害血管の再内皮化には影響せず、新生内膜形成を促進することを明らかとし、小骨髄細胞を動員するサイトカインを用いた血管再生療法の臨床応用には注意が必要であることを報告した。さらに、Ang-1 や EPO の骨髄幹細胞移植との併用が著明な血管新生効果を示すことを明らかとした。

## D. 考察

本研究により、ASO に比較してバージャー病のほうが骨髄幹細胞移植療法の治療効果が高く、治療効果も持続することが明らかとなった。一方、膠原病症例では、疾患そのものが比較的稀であり本治療法の適応となる症例が少ないことや膠原病の原疾患そのものも違いがあることから、その比較は困難である。しかし、強皮症では全例で本治療法が有効であることから、強皮症による難治性皮膚潰瘍に対する有効な治療法となる可能性が示された。今後の検討すべき課題としては、症例数の増加と共に膠原病の原疾患そのものによる違いやステロイド服用下での有効性、長期的な有効性と有害事象の解析などがある。特に、血管炎が活動期にある場合には細胞移植によりさらに炎症を増悪させる可能性があることから、どのような血管炎に、あるいはどのような炎症の状態の場合に本治療法を施行して良いのか、ステロイドはどこまで減量してから本治療法を行った方がよいのかといった問題は早急に解明する必要がある。また、基礎的研究ではG-CSFやEPO、Ang-1などによる

血管新生効果が示され、今後、これらの因子を用いた治療による患者負担の減少とより効果的な血管新生治療法の確立が期待される。一方、単球系の骨髄細胞を動員させるM-CSFは血管傷害後の血管修復には影響せず、逆に新生内膜形成を促進したことから、サイトカインを用いた骨髄細胞動員療法の臨床応用にはさらに詳細な機序の解明や条件検討が必要であると考えられる。

## E. 結論

バージャー病や膠原病による難治性血管炎による指趾の血行障害を有する患者に対して、自己骨髄幹細胞移植による血管再生療法の多施設臨床試験を行い、その有効性と安全性を検証した。また、本治療法の作用機序の解明とより侵襲が少なく患者さんに優しい治療法の開発を目的として、サイトカイン投与による骨髄幹細胞動員療法の有効性についても検討した。本研究により、難治性血管炎に対する日本発の新たな治療法が確立されるものと期待される。

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