C. 難治性頻回再発型・ステロイド依存性ネフローゼ症候群の治療

CQ 3’

clinical question

小児期発症難治性頻回再発型・ステロイド依存性ネフローゼ症候群に対するリツキシマブ療法の後療法としてミコフェノール酸モフェチル投与は推奨されるか

ステートメント

- 小児期発症難治性頻回再発型・ステロイド依存性ネフローゼ症候群に対するリツキシマブ療法の後療法として，寛解維持のためにミコフェノール酸モフェチルを投与することを提案する（適応外使用）．**推奨グレード 2B（一致率 88%）**

治療例

リツキシマブ投与後から，ミコフェノール酸モフェチルを 1,000 ～ 1,200 mg/m^2/日（最大投与量 2 g/日）分 2 で投与する．

エビデンスの要約

小児期に特発性ネフローゼ症候群を発症しステロイド感受性を示すものの，既存治療（ステロイド，免疫抑制薬など）では寛解が維持できず頻回再発型あるいはステロイド依存性を呈する難治性のネフローゼ症候群に対するリツキシマブ療法の後療法としてミコフェノール酸モフェチルを使用することが寛解維持に臨床的に有効であることが，わが国のランダム化比較試験で示された．リツキシマブ療法とともに十分な知識・経験を持つ医師のもとで使用する．

解　説

前項 CQ3 でも示されているように，小児期発症難治性頻回再発型・ステロイド依存性ネフローゼ症候群に対して，わが国をはじめとする複数のランダム化比較試験[1-3]の結果，リツキシマブの有効性が示されている．一方で，わが国で行われたランダム化比較試験[1]の長期予後調査では，リツキシマブを 1 週間間隔で計 4 回投与した難治性頻回再発型・ステロイド依存性ネフローゼ症候群患者 51 人の観察期間中央値 59 か月の結果として，48 人（94%）が再発し，50% 無再発期間は 261 日であったと報告[4]され，リツキシマブ治療後に長期寛解を維持する治療法の確立が望まれていた．

リツキシマブ治療の後療法としては，2009 年に Kamei らによって行われた小児期発症難治性ステロイド依存性ネフローゼ症候群に対するリツキシマブ単回投与の観察研究（n=12 人）[5]の結果で，後療法としてミコフェノール酸モフェチルを用いていた 3 人のうち 2 人が長期寛解を維持したと報告され、リツキシマブの後療法としてのミコフェノール酸モフェチルの可能性が示唆された．この結果をふまえ，Ito らはリツキシマブの後療法としてミコフェノール酸モフェチルを投与し，リツキシマブの総投与回数の減少と無再発期間の延長を目指

したパイロット研究を日本人患者 16 人を対象として行い、リツキシマブ投与後の平均再発回数(回/年)は，リツキシマブ 1 回投与＋ミコフェノール酸モフェチル 1 年間併用群 9 例のほうがリツキシマブ 1 回投与群 7 例よりも有意に少ないことを示した(0.4 回/年 vs. 2.3 回/年，$p < 0.005$)[6]．重篤な有害事象も認められず，ミコフェノール酸モフェチルはリツキシマブの後療法として有用であると考えられ，わが国で小児難治性頻回再発型・ステロイド依存性ネフローゼ症候群に対するリツキシマブ治療後の寛解維持療法としてのミコフェノール酸モフェチルの有効性と安全性を評価するための多施設共同二重盲検プラセボ対照ランダム化比較試験(JSKDC07 試験，UMIN 試験 ID：UMIN000014347，jRCT 臨床研究実施計画番号：jRCTs051180081)」[7,8]が行われるにいたった．

本臨床試験は，小児期発症難治性頻回再発型・ステロイド依存性ネフローゼ症候群患者を対象として，寛解維持療法としてリツキシマブを 375 mg/m^2/回(最大投与量 500 mg/回)を 1 週間間隔で計 4 回点滴静注した後に，ミコフェノール酸モフェチルもしくはプラセボを 1,000 ～ 1,200 mg/m^2/日(最大投与量 2 g/日)分 2 を 17 か月間経口投与し，その有効性と安全性を評価している(各群 43 名ずつ，計 86 名が参加)．主要評価項目の試験治療期間及び追跡期間を通じて(ミコフェノール酸モフェチル投与終了後の経過を含む)の treatment failure*発生までの期間の中央値は，ミコフェノール酸モフェチル群は 784.0 日，プラセボ群で 472.5 日と，ミコフェノール酸モフェチル群の方が長かったものの，統計学的な有意差は認められなかった(p=0.0694)．しかし、事後解析ではあるが，試験治療期間中(ミコフェノール酸モフェチルならびにプラセボ内服中)の treatment failure 発生までの期間の中央値は，ミコフェノール酸モフェチル群は未到達，プラセボ群で 493.0 日であり，ミコフェノール酸モフェチル群のプラセボ群に対するハザード比は 0.202(p=0.0001)と treatment failure 発生を 80% 抑制した．さらに副次評価項目である試験治療期間中の再発回数は，ミコフェノール酸モフェチル群ではプラセボ群に比して有意に少なく(平均 ± 標準偏差：0.43 ± 0.90 vs. 1.99 ± 2.37 回/人・年，ハザード比：0.257，95% 信頼区間：0.084-0.480)，試験治療期間中のステロイド投与量も有意に減少した(平均 ± 標準偏差：4.45 ± 3.52 vs. 10.45 ± 12.49 mg/m^2/日，p=0.0004)．また有害事象に関しては，治療を要した感染症がミコフェノール酸モフェチル群に多かった(1.59 回 vs 0.82 回，平均比：1.94(95% 信頼区間 1.07-3.52))が，infusion reaction ならびに遅発性好中球数減少の頻度に差はなく，死亡例もなく，安全性は許容範囲であった．以上の結果から，著者らは，統計的には証明されなかったが，リツキシマブ治療後のミコフェノール酸モフェチル維持療法は，小児期発症難治性頻回再発型・ステロイド依存性ネフローゼ症候群の寛解を維持するための選択肢となり得ると結論している．したがって，小児期発症難治性頻回再発型・ステロイド依存性ネフローゼ症候群に対するリツキシマブ療法の後療法としてミコフェノール酸モフェチル投与を提案するとし，推奨グレード 2B とした．

他の免疫抑制薬(シクロフォスファミド，シクロスポリン，タクロリムスなど)では小児期発症難治性頻回再発型・ステロイド依存性ネフローゼ症候群へのリツキシマブ治療の後療法としてのプラセボ対照ランダム化比較試験は行われていない．また，リツキシマブ治療の後療法としてのミコフェノール酸モフェチルと他の免疫抑制薬の優劣を比較した試験は，シクロスポリンとミコフェノール酸モフェチルを比較した少数例の前向き非ランダム化試験[9]があるが，今のところその優劣を論じるだけの根拠に乏しい．

リツキシマブ治療後に長期寛解を維持する他の手段として，リツキシマブの反復投与がある[10]．小児において，リツキシマブを反復投与することによる長期にわたるB細胞枯渇の安全性は現時点では不明であり，治療としては議論の余地がある．

＊：treatment failure
JSKDC07試験では，観察期間中に発生した①頻回再発，②ステロイド依存性，③ステロイド抵抗性と定義している．

文献

1）Iijima K et al. ; Rituximab for Childhood-onset Refractory Nephrotic Syndrome（RCRNS）Study Group : Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet 2014 ; 384 : 1273-1281

2）Ravani P, et al. : Short-term effects of rituximab in children with steroid- and calcineurin-dependent nephrotic syndrome : a randomized controlled trial. Clin J Am Soc Nephrol 2011 ; 6 : 1308-1315.

3）Ahn YH, et al.. Efficacy and safety of rituximab in childhood-onset, difficult-to-treat nephrotic syndrome: A multicenter open-label trial in Korea. Medicine（Baltimore）. 2018 : 97 : e13157.

4）Kamei K, et al. : Rituximab for Childhood-Onset Refractory Nephrotic Syndrome（RCRNS）Study Group : Long-term outcome of childhood-onset complicated nephrotic syndrome after a multicenter, double-blind, randomized, placebo-controlled trial of rituximab. Pediatr Nephrol 2017 ; 32 : 2071-2078.

5）Kamei K, et al. : Single dose of rituximab for refractory steroid-dependent nephrotic syndrome in children. Pediatr Nephrol 2009 ; 24 : 1321-1328

6）Ito S, et al. : Maintenance therapy with mycophenolate mofetil after rituximab in pediatric patients with steroid-dependent nephrotic syndrome. Pediatr Nephrol 2011 ; 26 : 1823-1828

7）Horinouchi T, et al : Study protocol : mycophenolate mofetil as maintenance therapy after rituximab treatment for childhood-onset, complicated, frequently-relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome : a multicenter double-blind, randomized, placebo-controlled trial（JSKDC07）. BMC Nephrol 2018 ; 19 : 302

8）Iijima K, et al. : Mycophenolate Mofetil after Rituximab for Childhood-onset Complicated Frequently-relapsing or Steroid-dependent Nephrotic Syndrome. J Am Soc Nephrol. 2022 ; 33 : 401-419.

9）Fujinaga S, et al. : Cyclosporine versus mycophenolate mofetil for maintenance of remission of steroid-dependent nephrotic syndrome after a single infusion of rituximab. Eur J Pediatr 2013 ; 172 : 513-518.

10）Chan E, et al. : Long-term Efficacy and Safety of Repeated Rituximab to Maintain Remission in Idiopathic Childhood Nephrotic Syndrome : An International Study. J Am Soc Nephrol. 2022 ; 33 : 1193-1207.

CQ3*

Is mycophenolate mofetil treatment recommended as a rituximab after-treatment for childhood-onset refractory frequently-relapsing and steroid-dependent nephrotic syndrome?

Statement

We propose mycophenolate mofetil to be administered for remission maintenance as an after-treatment for rituximab therapy for childhood-onset refractory frequently-relapsing and steroid-dependent nephrotic syndrome (off-label use).

Recommendation grade 2B (agreement ratio 88%)

Treatment example

Following rituximab treatment, mycophenolate mofetil is administered at 1,000-1,200 mg/m^2/day (maximum dose 2 g/day) in two divided doses.

Evidence summary

A randomized comparative study conducted in Japan suggested that use of mycophenolate mofetil as an after-treatment for rituximab therapy might be clinically effective in remission maintenance for intractable nephrotic syndrome that develops as idiopathic nephrotic syndrome in childhood, shows steroid sensitivity, does not respond to conventional treatments (steroids, immunosuppressants, etc.) to maintain remission, and shows frequent relapses or steroid dependency. This treatment should be administered by a physician with adequate knowledge and experience.

Commentary

Three randomized comparative studies [1-3], including the Japanese study described in the foregoing section, CQ3, demonstrated efficacy of rituximab for childhood-onset refractory frequently-relapsing and steroid-dependent nephrotic syndrome. On the other hand, a long-term prognosis survey in a Japanese randomized comparative study [1] reported that out of 51 patients with refractory frequently-relapsing and steroid-dependent nephrotic syndrome who received a total of four doses of rituximab at 1-week intervals during a median observation period of 59 months, 48 patients (94%) experienced relapses, with a 50% relapse-free time of 261 days [4]; there has been demand for the establishment of a treatment to maintain long-term remission following rituximab treatment.

Regarding after-treatment in rituximab therapy, an observational study conducted by Kamei et al. in 2009 in 12 patients receiving a single dose of rituximab for childhood-onset refractory and steroid-dependent nephrotic syndrome [5] reported that 2 of 3 patients on an after-treatment

with mycophenolate mofetil maintained remission for a long time, suggesting the potential use of mycophenolate mofetil as a rituximab after-treatment. With this result in mind, Ito et al. conducted a pilot study in 16 Japanese patients receiving mycophenolate mofetil as a rituximab after-treatment, with the aim to reduce the total number of rituximab doses and prolong the relapse-free time, showing that the mean number of relapses/year following rituximab treatment was significantly smaller in 9 patients receiving a single dose of rituximab in combination with mycophenolate mofetil for 1 year than in 7 patients receiving a single dose of rituximab (0.4 relapses/year vs. 2.3 relapses/year, $p<0.005$) [6]. With no serious adverse event observed, mycophenolate mofetil was considered to be useful as a rituximab after-treatment, and a multicenter double-blind placebo-controlled randomized comparative study (Study JSKDC07, University Hospital Medical Information Network Clinical Trials Registry ID UMIN000014347, Japan Registry of Clinical Trials Clinical Study Protocol No. jRCTs051180081) was conducted to evaluate the efficacy and safety of mycophenolate mofetil as a remission maintenance therapy following rituximab treatment for pediatric refractory frequently-relapsing and steroid-dependent nephrotic syndrome in Japan [7,8]. This clinical study evaluated the efficacy and safety of mycophenolate mofetil versus placebo administered orally at 1,000 to 1,200 mg/m^2/day (maximum dose 2 g/day) in two divided doses a day for 17 months following a total of four intravenous doses of rituximab at 375 mg/m^2/dose (maximum dose 500 mg/dose) at 1-week intervals as remission maintenance therapy, in patients with childhood-onset refractory frequently-relapsing and steroid-dependent nephrotic syndrome (each group consisting of 43 patients, a total of 86 patients participating in the evaluations). The median of the primary endpoint, i.e., time to onset of treatment failure* throughout the study treatment period and follow-up period (including the course following the end of mycophenolate mofetil treatment), was 784.0 days in the mycophenolate mofetil group and 472.5 days in the placebo group; although the median time was longer in the mycophenolate mofetil group, the difference was not statistically significant ($p=0.0694$). Post-hoc analysis showed, however, that the median time to onset of treatment failure during the study treatment period (with oral mycophenolate mofetil and placebo) was not reached in the mycophenolate mofetil group and was 493.0 days for the placebo group, with a hazard ratio of 0.202 ($p=0.0001$) in the mycophenolate mofetil group compared with the placebo group; occurrences of treatment failures were suppressed by 80%. Furthermore, a secondary endpoint, i.e., the number of relapses during the study treatment period, was significantly smaller in the mycophenolate mofetil group than in the placebo group (mean ± standard deviation 0.43±0.90 vs. 1.99±2.37 relapses/person-year; hazard ratio 0.257; 95% confidence interval 0.084-0.480), and the steroid dose during the study treatment period also decreased significantly (mean ± standard deviation 4.45±3.52 vs. 10.45±12.49 mg/m^2/day; $p=0.0004$). As for adverse events, the number of infection events that required treatment was

larger in the mycophenolate mofetil group (1.59 vs 0.82, mean ratio 1.94 [95% confidence interval 1.07-3.52]). However, there was no significant difference in the frequency of infusion reactions or late onset neutropenia, nor was there any death; the safety was acceptable. Based on the above results, the present authors concluded that mycophenolate mofetil maintenance therapy following rituximab treatment could be an option for maintaining remission in childhood-onset refractory frequently-relapsing and steroid-dependent nephrotic syndrome, although no statistical evidence was obtained. Therefore, we decided to propose mycophenolate mofetil treatment as a rituximab after-treatment for childhood-onset refractory frequently-relapsing and steroid-dependent nephrotic syndrome, with the recommendation grade 2B.

With other immunosuppressants (cyclophosphamide, cyclosporin, tacrolimus, etc.), no placebo-controlled randomized comparative study has been conducted in childhood-onset refractory frequently-relapsing and steroid-dependent nephrotic syndrome as an after-treatment for rituximab treatment. In addition, a prospective non-randomized study of after-treatment following rituximab treatment was conducted in a few patients comparing mycophenolate mofetil and another immunosuppressant, cyclosporin [9]; however, evidence to determine which is better is lacking.

Another means of maintaining remission for a long time following rituximab treatment is repeated-dose administration of rituximab [10]. At present, the safety of repeated-dose administration of rituximab in terms of long-term B cell depletion in children is unclear and remains disputable as a treatment.

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*Treatment failure

In Study JSKDC07, treatment failure was defined as any of I) frequent relapses, II) steroid dependency, or III) steroid refractoriness during the observation period.

References

1) Iijima K et al. ; Rituximab for Childhood-onset Refractory Nephrotic Syndrome (RCRNS) Study Group : Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet 2014 ; 384 : 1273-1281

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5) Kamei K, et al. : Single dose of rituximab for refractory steroid-dependent nephrotic syndrome in children. Pediatr Nephrol 2009; 24: 1321-1328
6) Ito S, et al. : Maintenance therapy with mycophenolate mofetil after rituximab in pediatric patients with steroid-dependent nephrotic syndrome. Pediatr Nephrol 2011; 26: 1823-1828
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9) Fujinaga S, et al. : Cyclosporine versus mycophenolate mofetil for maintenance of remission of steroid-dependent nephrotic syndrome after a single infusion of rituximab. Eur J Pediatr 2013 ; 172 : 513-518.
10) Chan E, et al. : Long-term Efficacy and Safety of Repeated Rituximab to Maintain Remission in Idiopathic Childhood Nephrotic Syndrome: An International Study. J Am Soc Nephrol. 2022; 33: 1193-1207.

Literature queries

CQ 3 ‘: Is mycophenolate mofetil treatment recommended as a rituximab after-treatment for childhood-onset refractory frequently-relapsing and steroid-dependent nephrotic syndrome?

- **PubMed** (searched on August 14, 2022)

#1 "Nephrotic Syndrome"[TW]
#2 dependent[TIAB]
#3 frequent*[TIAB] AND relaps*[TIAB]
#4 SSNS[TIAB] OR FRNS[TIAB] OR SDNS[TIAB]
#5 refractory[TIAB]
#6 sensitive[TIAB]
#7 #2 OR #3 OR #4 OR #5 OR #6

#8 #1 AND #7
#9 "Rituximab"[TW] OR rituxan[TIAB]
#10 #8 AND #9
#11 #10 AND (child*[TW] OR infant*[TW] OR boy*[TW] OR girl*[TW] OR pediatric*[TW] OR paediatric*[TW] OR adolescen*[TW])
#12 #11 AND 2018[PDAT] : 2022[PDAT]
One-hundred-fourteen (114) search results

- ***Igaku Chuo Zasshi* website** (searched on August 14, 2022)

#1 (Nephrotic syndrome/TH or nephrotic syndrome/AL)
#2 (Rituximab/TH or rituximab /AL)
#3 Rituxan/AL
#4 rituxan/AL
#5 #2 or #3 or #4
#6 #1 and #5
#7 (#6) and (PT=meeting minutes excluded, CK=humans)
#8 (#7) and (CK=neonates and infants [1-23 months], young children [2-5 years], children [6-12 years], adolescents [13-18 years])
#9 (children/TH or children/AL)
#10 #7 and #9
#11 #8 or #10
#12 (#11) and (DT=2018:2022)
Sixty-two (62) search results

- **The Cochrane Library** (searched on August 14, 2022)

#1 MeSH descriptor: [Nephrotic Syndrome] this term only
#2 MeSH descriptor: [Nephrosis, Lipoid] this term only
#3 nephrotic syndrome
#4 lipoid nephrosis
#5 #1 or #2 or #3 or #4
#6 child* or infant* or boy* or girl* or pediatric* or paediatric* or adolescen*
#7 #5 and #6
#8 dependent
#9 frequent*
#10 relapse*
#11 SDNS
#12 FRNS
#13 SSNS
#14 refractory
#15 sensitive
#16 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17 Rituximab
#18 MeSH descriptor: [Rituximab] explode all trees
#19 #17 or #18
#20 #7 and #16 and #19
#21 #7 and #16 and #19 with Cochrane Library publication date between Jan 2018 and Aug 2022, in Cochrane Reviews, Cochrane Protocols
Seven (7) search results (The Cochrane Database of Systematic Review: CDSR)
#22 #7 and #16 and #19 with Publication year from 2018 to 2022, in Trials
Forty-seven (47) search results (The Cochrane Controlled Trials Register: CCTR)

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