Treatment of Primary FSGS in Adults

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ABSTRACT

Over the last 20 years, primary FSGS has emerged as one of the leading causes of idiopathic nephrotic syndrome in adults, particularly among African Americans. In nephrotic patients, progression to ESRD often occurs over the course of 5–10 years, whereas non-nephrotic patients and those entering a remission have an extremely favorable prognosis. As a result, it is in patients who remain persistently nephrotic despite conservative therapy that a more aggressive therapeutic approach is taken. Primary FSGS was once considered an entity nonresponsive to prednisone or immunosuppressive agents, but it has become apparent over the last 20 years that a substantial portion of nephrotic adults with primary FSGS do respond to treatment with a significantly improved prognosis. The recent histologic classification proposed for FSGS has provided additional insights into the prognosis and response to therapy. This article reviews the current knowledge regarding the presentation, prognosis, and therapeutic approach in adults with primary FSGS.


Primary FSGS has become one of the most common causes of idiopathic glomerular disease in adults. The incidence of primary FSGS has increased by 3- to 13-fold during the last 20–30 years, and the disease now accounts for 20%–25% of adult patients undergoing biopsy for evaluation of idiopathic GN; as a result the incidence is almost equal to that of IgA nephropathy and twice that of membranous GN. Among adults undergoing biopsy for evaluation of idiopathic nephrotic syndrome, FSGS is now the most common lesion as well, being seen in up to 35% of patients overall and in up to 80% of African American patients; that rate is two to three times the prevalence in white patients.

Because FSGS is a progressive form of renal disease, it has also become the most common cause of GN-related ESRD. The proportion of patients with ESRD attributed to FSGS was reported to be 2.3%, compared with 0.4% for membranous GN and 0.3% for IgA nephropathy.

The proportion of African American patients affected was again higher, with an incidence of 3% compared with 2% for white patients, and the annual incidence rate was 24 cases per million in African American individuals versus 5 cases per million in the white population. Thus, FSGS has become an increasingly important cause of renal disease and ESRD in adult patients in the United States and in African Americans in particular.

Primary FSGS is a diagnosis of exclusion because the lesion of FSGS merely represents a pattern of injury and provides no real insight into pathogenesis. A pathogenic classification of FSGS (Table 1) has been proposed: (1) cases due to injury secondary to reduced nephron mass or functional adaptations, hereditary basement membrane defects, or focal proliferative GN and (2) cases resulting from primary alterations of glomerular epithelial cells. FSGS due to primary alterations of glomerular epithelial cells can be a result of viral infection (HIV-associated nephropathy, hepatitis C virus infection, and infection-associated parvovirus B19 infection); drugs (heroin, lithium, anabolic steroids, and pamidronate); or genetic disorders (which may be familial or sporadic in nature). In addition, by exclusion, it can be idiopathic (primary) in nature.

Although the pathogenesis of primary FSGS has been suggested to be due to a circulating permeability factor, the actual factor has yet to be identified. Several candidate permeability factors have been entertained, such as cardiotrophin-like cytokine-1 and a circulating soluble urokinase receptor. It is important to consider and assess for secondary forms of FSGS because the presentation, prognosis, and therapeutic approach can differ substantially.

FSGS resulting from mutations of many proteins important in podocyte function, including podocin, α-actinin 4, and transient receptor potential channel 6, is an area of increasing interest. These mutations are most often associated with familial forms of FSGS, but sporadic mutations in podocin have been reported and the presentation can be indistinguishable from that of primary FSGS. Sporadic podocin mutations have been observed in up to 30% of children with steroid-resistant FSGS but are extremely rare in adults. Therefore, routine screening is not advocated.
in adults. Recently, patients with high-risk variants of two other proteins important in podocyte function—nonmuscle myosin heavy chain-9 and apolipoprotein L1—have been found to be at markedly increased risk of developing FSGS. These high-risk variants may be seen in up to 60% of African American patients but in less than 5% of European American patients, and it is felt that this difference may in part explain the excessive risk for FSGS and ESRD observed in African American patients.

**PRESENTING FEATURES AND PROGNOSIS OF PRIMARY FSGS**

Adults with primary FSGS present with proteinuria, which is in the nephrotic range (>3 g of protein/d) in more than 70% of cases. Hypertension, microscopic hematuria, and renal insufficiency are common, being seen in 30%–45% of cases at presentation. In patients with primary FSGS, the onset of the nephrotic syndrome is often relatively sudden, occurring over weeks and months. In other patients the presentation of the nephrotic syndrome is more indolent. These patients initially present with non-nephrotic proteinuria and over the course of months to years develop increasing proteinuria, often associated with worsening renal function, which becomes nephrotic in range.

However, such patients do not generally develop full-blown nephrotic syndrome with hypoalbuminemia or edema. This scenario is often seen in patients with secondary FSGS due to longstanding hypertension, morbid obesity, or reflux nephropathy, or in the setting of a solitary kidney due to congenital dysplasia and loss of nephron mass. Distinguishing patients with nephrotic-range proteinuria due to secondary forms of FSGS from primary FSGS is important because the prognosis and therapy can differ substantially.

The level of proteinuria has long been known to have prognostic significance in primary FSGS. Patients with non-nephrotic proteinuria have an extremely good prognosis; <15% progress to ESRD over the course of 10 years, whereas ≥50% of patients with nephrotic-range proteinuria progress to ESRD over 5–10 years. In patients with massive proteinuria (>10–14 g/d), the course is particularly malignant, resulting in ESRD by 2–3 years on average.

In nephrotic adults with FSGS, several clinical and histologic features at biopsy are predictive of progression to ESRD. These include serum creatinine level >1.3 mg/dl, interstitial fibrosis >20%, and the presence of collapsing lesions. However, the attainment of remission in nephrotic patients with FSGS is associated with a significantly reduced risk for progression to ESRD. Patients entering remission have an excellent prognosis, with a 10-year renal survival rate of >90%, compared with approximately <35% in patients not attaining remission. As shown by Troyanov et al., even a partial remission portends a good prognosis, with a 10-year renal survival rate of approximately 75%. Thus, attainment of remission is the ultimate goal in nephrotic patients with primary FSGS.

**INITIAL TREATMENT WITH CONSERVATIVE MEASURES**

In proteinuric patients with primary or secondary FSGS (both non-nephrotic and nephrotic), the initial approach is similar to that in other forms of primary glomerular diseases and consists of optimal BP control and the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs). In patients who become or remain non-nephrotic after 6 months of therapy, this remains the primary therapeutic approach. Although the use of ACE inhibitors or ARBs in nephrotic patients with FSGS results in a slower rate of progressive renal insufficiency and better renal survival, it is rare that severely nephrotic patients enter into partial or complete remission with conservative management alone. In addition, spontaneous remissions are rare in nephrotic patients with FSGS, occurring in <5% of patients. However, the use of prednisone or immunosuppressive therapy is associated with a significantly increased likelihood of a remission. It is therefore in patients who are persistently nephrotic after a course of conservative therapy or in patients presenting with complications from the nephrotic syndrome that more aggressive treatment with prednisone or immunosuppressive agents is recommended. Ultimately, the prognosis of these nephrotic patients with FSGS becomes defined by their response to prednisone/immunosuppressive therapy. In patients with nephrotic-range proteinuria due to secondary forms of FSGS (genetic causes, HIV-associated nephropathy, longstanding hypertension, morbid obesity, reflux nephropathy, loss of...
nephron mass), the mainstay of therapy remains BP control, ACE inhibitors and ARBs, and disease-specific treatment if available (e.g., retroviral therapy in HIV-associated nephropathy). The use of immunosuppressive agents is not beneficial, can be harmful, and is therefore not recommended in these settings.

**INITIAL IMMUNOSUPPRESSIVE TREATMENT AND RESPONSE IN NEPHROTIC PATIENTS**

The initial approach with immunosuppressive treatment for nephrotic adults with primary FSGS has most often consisted of high-dose steroids alone or in combination with a cytotoxic agent. This usually consists of oral prednisone at a dosage of approximately 1 mg/kg per day, and the duration of the high-dose therapy has generally been 2–3 months, with a taper extending for an additional 4 months. With use of this approach, overall remission rates of 47%–66% have been reported, with complete remission rates of 32%–47% and partial remission rates of 19%–29%. Although the level of proteinuria generally begins to decrease after 1–2 months of therapy, the median time to remission is 4–6 months. Ponticelli et al. found patients receiving steroids for >16 weeks had a 61% remission rate, compared with 15% in patients receiving ≤16 weeks of therapy. Rydel et al. reported that patients who entered remission had received a significantly longer period of high-dose therapy (3 months on average), with a total treatment duration, including taper, of 5 months compared to only 1 month of high-dose steroids, with a total of 3 months of treatment overall. As a result of this experience, it has been suggested that steroid resistance in nephrotic adults with FSGS is defined by the persistence of the nephrotic syndrome after a more prolonged course of therapy (4 months of prednisone at a dosage of 1 mg/kg per day). However, Cattran and Rao found that if a patient had not responded to steroids by 6 months, treatment beyond this duration was not beneficial.

The addition of a cytotoxic agent to prednisone as initial therapy has not been shown to improve the overall remission rate.

In an attempt to minimize the potential toxicity of daily high-dose steroids, a few studies have evaluated the use of high-dose, alternate-day steroid therapy. These studies have shown mixed results. In a study of only 10 patients, high-dose alternate-day therapy (60–120 mg every other day) given for up to 21 months resulted in no complete remissions. However, another study by Nagai et al. that assessed high-dose alternate-day therapy in elderly adults (>60 years of age) found that after 3–5 months of therapy, 44% attained a complete remission. Thus, an alternate-day approach appears to be beneficial in older patients with nephrotic FSGS.

Patients in whom the use of high-dose steroids is of particular concern (such as those with poorly controlled diabetes or morbid obesity) may be treated with calcineurin inhibitors or mycophenolate mofetil (MMF) as steroid-sparing alternatives. MMF as initial treatment in nephrotic adults with FSGS was assessed by Nayagam et al. in a randomized prospective trial. MMF was given at a dosage of 1 g twice daily for 6 months, along with low-dose steroids for 2–3 months in 17 patients, while 16 patients received prednisolone at 1 mg/kg per day for 3–6 months. The 70% remission rate in the MMF group was similar to the 69% response in the prednisolone group. The time to remission on average was 6 weeks in the MMF group and 10 weeks in the steroid group, and the relapse rates of 23% and 18%, respectively, were similar among the two groups; however, the total dose of steroids used was significantly lower than in the MMF group (2 versus 7 g). Thus, on the basis of this small study, MMF may provide a steroid-sparing alternative for initial therapy in nephrotic patients with primary FSGS.

**VALUE OF HISTOLOGIC CLASSIFICATION OF FSGS IN PREDICTING RESPONSE TO TREATMENT**

It would be ideal if there were a measure by which one could reliably predict which patients are most likely to benefit from steroids or immunosuppressive therapy in order to avoid exposing the patients least likely to respond to the potential side effects of this therapy. No clinical, laboratory, or histologic feature at baseline has been found to reliably predict who will respond to treatment. Additionally, the level of permeability factor activity does not predict response to therapy in primary FSGS, and although the fractional excretion of IgG was initially found to be predictive of steroid response in one study, it was not predictive in another. Thus, to date, there is no measure by which to predict response to steroids therapy in FSGS.

In 2003 D’Agati et al. proposed a histologic classification of FSGS to better characterize the various lesions associated with FSGS and better understand potential differences in presentation, prognosis, and response to therapy. This classification consists of five lesions, which include the classic lesion of FSGS (FSGS not otherwise specified) and four variants: perihilar, cellular, tip, and collapsing lesions. According to this classification, patients with the tip lesion appear to have the best prognosis and the highest likelihood of response to therapy, whereas patients with collapsing FSGS have the poorest prognosis and are less likely to enter remission.

Patients with tip and collapsing lesions present with nephrotic syndrome, often associated with massive proteinuria (>10 g/d); however, patients with the tip lesion are more often white (85% of the time) and have a relatively normal serum creatinine level, whereas patients with collapsing FSGS are more often African American (>90% of cases) and have more advanced renal insufficiency at the time of biopsy. In the study by Thomas et al., the remission rate was 18% for patients with collapsing FSGS compared with 53% in patients with the tip lesion; the renal survival rates at 3 years were 33% and 76%, respectively. Thus, it would appear that patients with the tip lesion would be those most likely to benefit from steroid therapy, whereas those with collapsing FSGS

**References**


2. Treatment of Primary FSGS in Adults 1771
would be the least likely to benefit. However, Deegens et al. found that FSGS lesion was not very predictive because patients with collapsing FSGS had a 40% remission rate, which was only slightly lower than the remission rate of 53% in patients with a tip lesion.

The response to therapy in patients with collapsing FSGS has ranged from as low as 12% to as high as 64%.

What becomes apparent upon review of the studies that report a remission rate of <20% is that the patients have more advanced renal insufficiency (serum creatinine level >3.5 mg/dl), collapsing lesions that are more widespread (>50% of glomeruli), and interstitial fibrosis ≥2+ in 60%–90% of patients compared to studies with higher remission rates. In the study by Chun et al., which noted a 64% remission rate in patients with collapsing FSGS, renal disease was less advanced with a creatinine level at biopsy of 2.5 mg/dl, only 22% of glomeruli having collapsing lesions and ≥2+ interstitial fibrosis being seen in only 50% of biopsy specimens. Thus, studies reporting a poor response to therapy had patients with more advanced renal insufficiency with histologic evidence of widespread disease and irreversible damage. Chun et al. reported a 92% (12 of 13 patients treated) remission rate in patients with collapsing lesions involving <20% of glomeruli, compared with only 33% (4 of 12 patients) in patients who had collapsing lesions in ≥20% of glomeruli. Thus, the more widespread the collapsing lesion, the poorer the likelihood of response; however, even then 33% of patients with widespread involvement attained remission. Thus, the presence of the collapsing lesion alone is not universally predictive of a poor response to treatment.

In contrast to collapsing FSGS, patients with a tip lesion are extremely responsive to therapy and have an excellent renal survival. Chun et al. found that patients with a tip lesion had a remission rate of 78%. This was similar to the 72% remission rate observed by Stokes et al. In addition, patients with a tip lesion were far more likely to have a complete remission (56%–58%) than patients with collapsing FSGS (24%) or classic FSGS not otherwise specified (35%). Although patients with a tip lesion who attain remission have an excellent renal survival, the prognosis for patients who do not respond to therapy is quite poor. Chun et al. found the 5-year renal survival rate was only 25% in patients with a tip lesion who did not attain remission compared with 100% in those who did. Howie et al. made the additional observation that the prognosis for patients with a tip lesion was significantly worse when segmental sclerosing lesions were also found in the biopsy specimen. In patients with a pure tip lesion (no glomeruli with segmental scars), the response to treatment and prognosis was excellent, with a complete remission rate of 77% and 10-year renal survival rate of 94%. However, in patients whose biopsy specimens showed both tip lesions and glomeruli with segmental scars, no patient entered complete remission and the 10-year renal survival was only 53%. Thus, patients with a tip lesion seem to represent a heterogeneous group: The lesion behaves like minimal-change disease in some patients and more like FSGS in others.

Unfortunately, it is impossible to distinguish which patients with a tip lesion are most likely to have a favorable course, and thus the response to treatment remains the best predictor of outcome. Although the histologic classification of FSGS has provided important insights into the presentation and course of FSGS, it does not allow one to accurately predict who will or will not respond to therapy.

TREATMENT OF STEROID-RESPONSIVE/RELAPSING FSGS

Relapse of the nephrotic syndrome in adults with FSGS occurs in 25%–36% of patients after a complete remission and in more than 50% of patients with partial remissions. The time to relapse after a complete remission ranges from 20 to 36 months. Although the renal survival for patients who have remission and then relapse is significantly better than for patients who never achieved remission, the rate of loss of renal function is significantly greater and the risk for renal failure is higher than in patients remaining in remission. Thus, the ultimate goal is an attempt to reattain and maintain remission if possible.

The treatment options for relapsing FSGS are similar to those used for relapsing minimal-change disease. These include another course of steroids, the use of cytotoxic agents (cyclophosphamide, chlorambucil, or MMF) or calcineurin inhibitors (cyclosporine A [CSA] or tacrolimus). One could opt to treat a second time with steroids and tapering the dose more slowly in an attempt to sustain a longer remission. The use of cytotoxic agents such as cyclophosphamide or calcineurin inhibitors provides an alternative to another, more prolonged course of steroid therapy. Overall the response to therapy is excellent in steroid-responsive patients, with remission rates of 75%–80%.

As in minimal-change disease, the advantage to using cyclophosphamide is a more prolonged remission, whereas CSA can result in relapse after discontinuation. In a randomized, controlled trial, Ponticelli et al. compared oral cyclophosphamide (2.5 mg/kg per day) given for 2 months with CSA (5–6 mg/kg per day in two divided doses) given for 9 months in 66 patients with steroid-dependent, frequently relapsing nephrotic syndrome who were in remission while receiving prednisone. The prednisone dose was tapered off within 5 months of study entry, and at 9 months, the number of patients who had relapsed in the cyclophosphamide group was similar to that of the CSA group (33% versus 25%). However, by 24 months 75% of patients in the CSA group had relapsed compared with 37% of patients in the cyclophosphamide group. Thus, the increased relapse rate after the discontinuation of CSA results in the need for ongoing CSA use and often CSA dependence, with the associated increased risk for nephrotoxicity. It has been suggested that in FSGS, the antiproteinuric effect of calcineurin inhibitors may actually be due to a direct effect on the cytoskeleton of podocytes,
and it has been shown that the antiproteinuric effect of CSA is independent of the level of permeability factor activity.62–64 These observations help explain why patients responding to treatment with calcineurin inhibitors may relapse when the drug dose is tapered.

MMF has also been beneficial in the treatment of steroid-responsive FSGS.65–68 As with CSA, patients may relapse when the drug dose is tapered, and the actual dose and duration of therapy required to sustain long-term remission have not been determined.

TREATMENT OF STEROID-RESISTANT FSGS

Steroid-resistant patients with FSGS are of greatest concern to nephrologists because this group of patients is at significant risk for ongoing progression of renal disease. Overall, the response to cytotoxic therapy in steroid-resistant adults with FSGS is poor, at around 18%–22%; the response to CSA is better, at almost 70%.22,69,70 The use of low-dose prednisone with CSA may enhance the likelihood of remission.71 In general, if a response to CSA is not observed after 4–6 months of therapy, it is unlikely to occur.72–74

In two randomized, controlled trials assessing the use of CSA in steroid-resistant FSGS, remission rates of 57% and 69% were reported.69,70 The largest of these studies, by Cattran et al.,69 was conducted in 49 steroid-resistant nephrotic adults with FSGS. All received prednisone at 0.15 mg/kg per day; 26 patients were randomly assigned to CSA at 3.5 mg/kg per day in two divided doses, and 23 patients were randomly assigned to placebo. Patients receiving CSA were titrated to a 12-hour trough level of 125–225 μg/L and were treated for 6 months; the CSA dose was then tapered off over 1 month.

The remission rate at 6 months was 69% in the CSA group, with 12% of patients attaining a complete remission and 57% attaining a partial remission, compared with an overall remission rate of <5% in the placebo group. The average time to remission was 7 weeks (range, 1–25 weeks). However, by 78 weeks 60% of patients in the CSA group had relapsed. Nonetheless, the renal survival for patients in the CSA group was significantly better; a 50% decline in creatinine clearance at 4 years was observed in only 25% of CSA-treated patients compared with 52% of the placebo group (P<0.05). On the basis of these findings, a 6-month course of CSA has become the standard treatment for nephrotic adults with steroid-resistant FSGS. Because of the high relapse rate observed after discontinuing CSA, many nephrologists would continue CSA treatment for a more prolonged period; however, there is always the concern of CSA nephrotoxicity.

Meyrier et al.41 studied CSA nephrotoxicity in a group of patients with FSGS who had baseline and follow-up renal biopsies performed after 12 months of treatment with CSA. According to the follow-up biopsy results, they found that the risk for nephrotoxicity was generally seen at 11–29 months and was greatest in patients whose CSA dosage was >5.5 mg/kg per day. They also found that among patients who remained in remission while receiving CSA treatment for more than 12 months, the CSA dose could then be successfully tapered off without relapse. Bagnis et al.75 studied the long-term renal effects of using low-dose CSA in patients being treated for uveitis. They found the increase in serum creatinine was significantly smaller over the course of 2 years in patients receiving CSA at a dosage $\leq 3$ mg/kg per day than that in patients receiving $>3$ mg/kg per day (0.09 versus 0.32 mg/dl; P<0.003), and repeat renal biopsies performed after 2 years of CSA demonstrated evidence of less nephrotoxicity in patients receiving the lower doses.

To maintain remission and minimize the potential for CSA nephrotoxicity, it has been suggested that once a complete remission has been achieved, the CSA dose should be slowly tapered by 0.5 mg/kg per month to the lowest effective dose.74 After remission is maintained for 1–2 years with low-dose CSA, an attempt to taper off CSA altogether is recommended. If no response to CSA has been demonstrated by 6 months of treatment (at least ≥50% reduction in baseline proteinuria), CSA should be discontinued and another therapeutic approach considered.

The use of tacrolimus in CSA-dependent or resistant FSGS was evaluated by Segarra et al.76 in an uncontrolled prospective study. They found the remission rate after 6 months of tacrolimus therapy was very much dictated by the initial CSA response, with an 83% remission rate in patients who were initially CSA responsive compared with a remission rate of only 15% in CSA-resistant patients. The mean time to remission was 4 months, and the relapse rate was 76% within 1–4 months of discontinuing tacrolimus. Although tacrolimus may be an alternative to CSA, it appears to have a similar profile.

Cattran et al.77 assessed MMF in 18 nephrotic adults with steroid-resistant FSGS. In 75% of them, treatment with cyclophosphamide and/or CSA had failed. MMF was given at a dosage of 1 g twice daily along with low-dose steroids for 6 months, and patients were followed for 1 year after treatment. At 6 months, 44% of patients had improvement in proteinuria, attaining a partial remission or a 50% reduction in proteinuria, but no patient achieved a complete remission. However, Segarra et al.78 evaluated MMF as a rescue therapy in 22 steroid-resistant FSGS patients and found that a complete or partial remission was obtained in 54% of patients. Thus, MMF may be an alternative in patients resistant to steroids or immunosuppressive therapy.

Recently, a prospective randomized, controlled trial compared the efficacy of CSA with that of MMF plus pulse dexamethasone in the treatment of 138 steroid-resistant children and adults with FSGS (age range, 2–40 years).79 Patients were treated for 12 months, and all patients received ACE inhibitors and alternate-day oral prednisone. The study found no significant difference in the combined complete and partial remission rates between the CSA and
MMF groups (44% versus 33%). Thus, MMF was not superior to CSA in inducing remission in patients with steroid-resistant FSGS.

Several other treatments have been tried in nephrotic patients with primary FGS who are steroid resistant. These have included plasmapheresis and protein adsorption columns, pulse dexamethasone, sirolimus, rituximab, oral galactose, and adrenocorticotropic hormone. To date these therapies have not been beneficial, or there is too little experience to determine their ultimate utility.

CONCLUSION

Primary FSGS is one of the most common causes of idiopathic nephrotic syndrome in adults. Many secondary causes of FSGS must be excluded. Non-nephrotic patients and nephrotic patients entering remission have a favorable outcome, whereas persistently nephrotic patients often progress to ESRD over 5–10 years. Initial therapy in all patients with FSGS should include ACE inhibitors or ARBs, along with good BP control. In patients who remain nephrotic despite the use of conservative measures, a course of prednisone at 1 mg/kg per day for a maximum of 16 weeks or until complete remission is attained (whichever comes first) is recommended. In patients attaining remission, steroids are then tapered slowly over 4–6 months. In patients for whom there is a concern about the use of steroids (patients with diabetes, obese patients, or those who cannot tolerate steroids), consider using calcineurin inhibitors or MMF as an initial therapy. In steroid-responsive patients who relapse, the treatment is similar to that of frequently relapsing or steroid-dependent minimal-change disease (cyclophosphamide, calcineurin inhibitors, or MMF). In steroid-resistant FSGS, a course of CSA at 3.5 mg/kg per day in divided doses can be given for 6 months, and if remission is attained, the dose should be slowly tapered to the lowest effective dose. After remission has been maintained for 1–2 years, CSA should be tapered off, if possible. Fortunately, with an aggressive approach, more than 50% of nephrotic adults with FSGS may attain remission with a significantly improved prognosis. Ideally, ongoing research will improve our understanding of the pathogenesis of primary FSGS, which will allow the development of more targeted therapies.

DISCLOSURES

S.M.K. has served as a consultant for TG Therapeutics, Inc.

REFERENCES


