Treatment of Susac’s Syndrome (SS)

Ideal Treatment of SS

Ideally, treatment of SS should be based on:
- An accurate understanding of the immunopathogenesis (cause) of the disease.
- An accurate understanding of the natural history and potential outcome of the disease.
- The results of controlled clinical trials.
- Individualized consideration of the risks of under-treatment versus the risks of over-treatment.

Unfortunately, our understanding of the immunopathogenesis of SS is quite incomplete. And, to date, our knowledge of the natural history and treatment of SS is based entirely on anecdotal case reports and retrospective analyses of short series of patients. No comprehensive, systematic and prospective study of the clinical features, clinical course, and treatment of SS has been conducted. No controlled studies of treatment have been conducted.

Accordingly, we need to do the best we can, with the information currently available—until collaborative study provides better information.

Immunopathogenesis of SS---Similar to that of Juvenile Dermatomyositis?

Current information suggests that the immunopathogenesis of SS may have much in common with that of juvenile dermatomyositis (JDM), an autoimmune endotheliopathy that affects the microvasculature of a different triad of tissues (muscle, skin, and gastrointestinal tract). The histopathologic and electron microscopic findings in the microvasculature of the brain and muscle of patients with SS are quite similar to the microvascular abnormalities seen in the skin and muscle of children with JDM. In both diseases the following microvascular abnormalities have been documented:
- endothelial cell swelling, sometimes to the point of lumenal occlusion
- endothelial cell degeneration and necrosis
- capillary network destruction (capillary "drop-out")
- basement membrane thickening, reduplication, and lamellation
- granular C5b-9 deposition in blood vessels
- perivascular lymphocytic infiltration

How, exactly, the immune system injures the endothelial cells in SS and in JDM is still unknown. Possibilities include:
- Production of antibodies against endothelial cells (anti-endothelial cell autoantibodies).
- Cytotoxic T cell attack on endothelial cells
- Cytokine mediated attack on endothelial cells
- Complement-mediated attack on endothelial cells.
Because JDM and SS both represent “autoimmune microvascular endotheliopathies,” and because the immunopathogenesis of these two diseases may be similar, JDM has appeared to represent an appropriate model for better understanding SS, including treatment of SS.

**Natural History of SS**

For a review of the natural history of SS, go to “About Susac's Syndrome: “Clinical Course” section.

**Historical treatment of SS**

Review of published case reports and case series has revealed a variable response of SS to immunosuppressive therapy. Some patients have improved without receiving any immunosuppressive treatment. This fact has tempted some to think that SS might not represent an autoimmune disease, or may not need immunosuppressive treatment.

The vast majority of reported patients have received corticosteroid therapy (prednisone, with or without pulses of intravenous methylprednisolone), and most have appeared to benefit, often promptly and dramatically. Many patients have been documented to quickly relapse during corticosteroid tapering, and most who have relapsed have responded to resumption or escalation of corticosteroid therapy.

However, some patients have failed to respond to high-dose oral prednisone (e.g., 80 mg/d for 2 months), probably because their disease was just too intense at that time. Most patients treated with Cyclophosphamide have improved, but there has been at least one report of Cyclophosphamide failure. Many patients have improved after receiving intravenous immunoglobulin (IVIG). Mycophenolate mofetil (MMF) and cyclosporine A have been used with success. Plasmapheresis has been successful in some patients but has also failed. Patients with severe disease have been successfully treated with a combination of high-dose corticosteroid, IVIG, and Cyclophosphamide.

This variation in the response of SS to immunosuppressive therapy is reminiscent of therapeutic experiences with JDM and is probably due, in part, to differences (between patients with the same disease) regarding disease severity, capacity for spontaneous remission, and propensity to relapse.

The potential for spontaneous and wide fluctuation of SS disease activity makes it difficult to interpret anecdotal responses to therapeutic interventions. Throughout treatment of SS, the physician must continually be prepared for spontaneous exacerbation or exacerbation due to a pace of medication tapering that exceeds the pace of immunologic self-correction.

Because there are important similarities between SS and JDM/DM, lessons learned about the immunopathogenesis, clinical course, and treatment of JDM may be applicable to SS. Accordingly, we have suggested that current and future treatment of SS be guided in part by experiences with JDM. One important difference between the two diseases, however, is that the brain, retina, and cochlea are more eloquent tissues than muscle and skin. Whereas patients with JDM/DM may be able to absorb a relapse of muscle disease without severe consequences, a relapse of SS is more likely to cause regrettable damage. Therefore, control of SS needs to be more complete, and prevention of relapse is more important.
JDM/DM responds to a variety of therapies: oral prednisone, pulses of methylprednisolone, IVIG, methotrexate, cyclosporine A, Cyclophosphamide, and MMF. The most recent additions to this list are sirolimus, anti–Tumor-Necrosis-Factor (anti-TNF) therapy, and rituximab.

During the 1950s and 1960s, treatment of JDM and DM tended to be delayed, insufficiently aggressive, and inadequately sustained, and the outcome was often poor. We have now learned that early, aggressive, and sustained treatment of JDM and DM results in much better outcome. We suspect that the same principle applies to SS.

Of the most recent treatments for JDM/DM, rituximab has received the most interest. Rituximab is a monoclonal antibody to CD20+ B cells. Since the CD20 marker is found on all mature B cells but not on stem cells or plasma cells, rituximab eliminates all mature B cells. It then takes 8 to 12 months for the patient’s stem cells to reconstitute the B-cell population. Rituximab therapy for DM and SS makes sense if aberrant B-cell behavior plays a key role in the pathogenesis of these diseases. In a pilot study, treatment of severe and recalcitrant DM with rituximab has been followed by dramatic clinical improvement.

Our recommendations (below) for “conventional” treatment of SS are based on limited experience with SS and more extensive experience with JDM/DM. They are not based on any controlled studies, because such studies have not been done. Accordingly, they should be viewed as suggestions, not as proven therapies based on strong medical evidence. They are primarily designed to treat SS with encephalopathy but also apply to treatment of patients without encephalopathy who are presenting with BRAO, hearing loss, or both (BRAO/HL). They may also apply to at least some patients who are experiencing frequently recurring episodes of BRAO/HL. All dosages shown are for adults.

Review of Immunologic Self-Correction and the Limitations of Current Treatments

Before discussing our current treatment recommendations, let’s review the principles of “immunologic self-correction” and the limitations of currently available treatments.

Immunologic Self-Correction

Fortunately, our immune systems are often able to correct their autoimmune mistakes—though it is apparently harder to self-correct some mistakes than others, and it appears that children have greater capacity for self-correction than do adults. For example, the immune systems of children usually are eventually able to correct the juvenile rheumatoid arthritis mistake, the juvenile dermatomyositis mistake, and even the lupus mistake; but, the immune system of adults usually has little success in correcting the rheumatoid arthritis mistake. Fortunately, the immune systems of adults and children seem to be able to self-correct the Susac’s Syndrome mistake, often within 1-3 years—though not always.

Limitations of Current Treatments

Unfortunately, we do not currently have treatments that can specifically and directly correct the immune mistake that an immune system is making. If we did, we would have a “cure” for that particular autoimmune disease. However, we do have treatments (immunosuppressive/anti-inflammatory treatments) that either
suppress the extent to which the immune system is making the mistake (by suppressing part or all of the immune system), or at least “throw water” on the fires that the immune system is mistakenly setting.

Until we have true “cures” for these autoimmune diseases, the main approach is to use immunosuppressive/anti-inflammatory medications to control the “autoimmune fires” (slow down the fire-setting and throw water on the fires that have already been set) until the person’s immune system is able to self-correct. If it is going to take the individual’s immune system 2 years to self-correct, that individual will need immunosuppressive treatment throughout those 2 years. Usually, self-correction occurs gradually, such that doses of immunosuppressive drugs can gradually be reduced after initial control has been achieved. But, the gradual reduction of immunosuppression needs to be done at a pace that is about equal to the pace of self-correction. If immunosuppressive treatment is reduced at a pace faster than the pace of self correction, a flare-up of disease is likely to occur.

Sometimes a person’s self-correction is interrupted by a return of loss of control (i.e. a relapse). In such an instance, the immunosuppressive doses that were working well, may no longer be sufficient and may need to be increased, at least temporarily.

**Treatment Recommendations/Options for Consideration**

The treatment guidelines provided on this website represent only preliminary and tentative recommendations. Multicenter, international collaborative study of the immunopathogenesis, clinical course, treatment, and outcome of a large number of patients with SS will be necessary to determine and confirm optimal treatment. In the meantime, we offer the following Treatment Graphs (Options) and comments for consideration:

The 13 Treatment Graphs (Options), below, visually summarize 13 treatment options for patients during their first year of treatment. We do not mean to suggest that these are the only options. They are meant to serve only as guidelines, as examples.

Variations of these options should, of course, be considered. For example, the corticosteroid exposure shown for Options 1, 4, 5 and 6 could be substituted for the corticosteroid exposure depicted for Options 7-12, and vice versa. Other creative “mixing and matching” would also be very appropriate—tailoring treatment to the specific circumstances and preferences of the patient and attending physician.

Ultimately, each patient should be treated according to the best clinical judgment of the attending physician, in conjunction with the informed preference of the patient/family.

**NOTE:**
- For Options 1-4 and 7-13, it would be very reasonable to use MMF from the very beginning (as is shown in Option 5) and not use cyclophosphamide at all.
- As mentioned above, the corticosteroid exposure shown for Options 1, 4, 5 and 6 could be substituted for the corticosteroid exposure depicted for Options 7-12, and vice versa.
- IVIG is used in all 13 treatment Options. This is because, anecdotally, IVIG has seemed to be very helpful for SS, and the risk/benefit ratio of IVIG is amongst the most attractive of any of our currently available immunosuppressive approaches. Although IVIG is very expensive, we feel it is worthy of frequent use for SS—especially because of the threatening nature of SS. Since SS is such a rare
disease, we feel it is appropriate and wise for insurance companies and government health care systems to approve IVIG for use in Susac’s syndrome.

Option #1

- Conventional PDN taper
- IVIG
- Prednisone mg/day
- MYCOPHENOLATE
- I = IVIG (2 Gm/kg)
- C = Cyclophosphamide Pulse
- | = Pulse Methylprednisolone (1 Gm)

Option #2

- Faster prednisone taper
- Prednisone
- MYCOPHENOLATE
- I = IVIG (2 Gm/kg)
- C = Cyclophosphamide Pulse
- | = Pulse Methylprednisolone (1 Gm)
Option # 3

Addition of monthly pulses of methylprednisolone, permitting more rapid PDN taper

Option # 4

Earlier conversion to mycophenolate

Treatment (PDF #7)
Susac’s Syndrome

Option # 5

**MYCOPHENOLATE**

Initial use of mycophenolate, instead of cyclophosphamide (CTX). Similarly, MMF could be used from the beginning, instead of CTX, in Options 1-4 and 7-13

- | = IVIG (2 Gm/kg)
- | = Pulse Methylprednisolone (1 Gm)

Option # 6

**MYCOPHENOLATE**

Addition of methotrexate to mycophenolate

- | = IVIG (2 Gm/kg)
- | = Pulse Methylprednisolone (1 Gm)
Susac’s Syndrome

Option #7

- **Mycophenolate**
  - Q wk
  - Q 2wk
  - Q 3wk
  - Q 4wk
- Reliance on frequent pulses of methylprednisolone and less prednisone

Pulse Methylprednisolone
- 3 pulses/wk
- 2 pulses/wk
- Q wk

Option #8

- **Mycophenolate MOFETIL**
  - Q wk
  - Q 2wk
  - Q 3wk
  - Q 4wk
- Reliance on frequent pulses, less prednisone, and less cyclophosphamide

Pulse Methylprednisolone
- 3 pulses/wk
- 2 pulses/wk
- Q wk
Susac's Syndrome

**Option # 9**

- **Mycophenolate**
  - Q wk  Q 2wk  Q 3wk  Q 4wk

- Frequent pulses of methylprednisolone and even more rapid tapering of prednisone

- Pulse Methylprednisolone
  - 3 pulses/wk  2 pulses/wk  Q wk

**Option # 10**

- **Mycophenolate MOFETIL**
  - Q wk  Q 2wk  Q 3wk  Q 4wk

- Addition of **Rituximab (RTX)**

- Pulse Methylprednisolone
  - 3 pulses/wk  2 pulses/wk  Q wk
Susac’s Syndrome

Option # 11

INFLIXIMAB

MYCOPHENOLATE MOFETIL

| C | C | C |

|------------------|

Q wk  Q 2wk  Q 3wk  Q 4wk

PREDNISONE

| 30 | 20 | 15 | 10 |

MOTHS  3  6  9  12

I = IVIG (2 Gm/kg)
C = Cyclophosphamide Pulse

Pulse Methylprednisolone

| 3 pulses/wk | 2 pulses/wk | Q wk |

Option # 12

PLASMA EXCHANGE

INFLIXIMAB

MYCOPHENOLATE MOFETIL

| C | C | C |

|------------------|

Q wk  Q 2wk  Q 3wk  Q 4wk

PREDNISONE

| 30 | 20 | 15 | 10 |

MOTHS  3  6  9  12

I = IVIG (2 Gm/kg)
C = Cyclophosphamide Pulse

Pulse Methylprednisolone

| 3 pulses/wk | 2 pulses/wk | Q wk |
All 13 options involve administration of 3-5 pulses of IV methylprednisolone during the first week (1 g in 100 mL D5W, infused over 2 hours). These pulses can be given on 3-5 consecutive days (20–24 hours apart). For more extreme cases, daily pulses could be given for a total of 5-8 consecutive days.

We recommend following the pulse methylprednisolone therapy with high-dose oral prednisone: 60 to 80 mg/d for the first 2 to 4 weeks, with plans to taper by approximately 10-15% every 2 weeks until the dose has been tapered to 20 mg each morning. Then taper more slowly (about 10% every 4 weeks) until down to 5 mg every morning, and eventually switch to 5 to 10 mg every other day. (We will subsequently refer to this as a “conventional tapering” schedule.) During the first 2 to 6 (usually 4) weeks of prednisone therapy, the daily dose can be given in two-three portions; thereafter, the daily dose should be consolidated into a single morning dose. (The split dosage, compared to a single AM dosage, provides for more disease suppression, but also causes more steroid side effects.)

The initial steroid dose and the pace of steroid tapering depend on several factors:
- The initial severity/intensity/tenacity of the disease
- How quickly and well the patient responds to initial therapy and initial tapering
- How much other immunosuppressive therapy the patient is receiving. (If cyclophosphamide, IVIG, frequent pulses of methylprednisolone, and/or rituximab are being relied upon, for example, less prednisone exposure will be necessary.)

Depending on the above factors, the initial pace of prednisone tapering could range from as slow as a 5% reduction (of the extant dose) every 2 weeks, to a 20% reduction every two weeks. Several prednisone
tapering options are depicted in the 13 Graphs---ranging from relatively rapid tapering (Option 2, 3, 7-12), to slow tapering (Option 13), with moderate, middle of the road tapering shown in Options 1,4-6.

We recommend starting IVIG (2 g/kg) during the first week of treatment, with plans to repeat this every 4 weeks for a total of at least six monthly treatments. For more severe, less responsive disease, a 2 g/kg dose of IVIG can be given every 2 weeks during the first 1 to 2 months---and, monthly IVIG could be given for more than 6 months. We prefer to give the 2 gm/kg over 2 days---half on the first day, the other half on the second day.

Within the first week or two, it is important to decide whether to use cyclophosphamide, MMF (mycophenolate mofetil), or azathioprine. For patients with threatening encephalopathic disease, cyclophosphamide might be most reliable---though, increasingly, MMF is appearing to be an appropriate alternative (based on recent experience with lupus).

For cyclophosphamide, we prefer IV pulses to oral therapy, and we recommend 3-7 monthly IV pulses (500mg/M2-750 mg/M2, with a maximum individual dose of 1.2 gm), according to the protocol established by the NIH for treatment of severe lupus (N Engl J Med 1986; 314: 614-19). However, for particularly threatening disease, an attractive alternative is to initially give smaller Q 2 week pulses of cyclophosphamide. For example, an IV pulse of cyclophosphamide could be given at a dose of 10-15 mg/kg (maximum dose 1.2 gm) Q 2 weeks x3, followed by a 10-15 mg/kg dose Q 3 weeks until the disease is solidly under control, then a Q 4 week schedule (Ann Intern Med 2009; 150: 670-680). After “induction” has been achieved (after 3-7 months of pulse cyclophosphamide therapy, e.g.), the patient can be placed on “maintenance” therapy, consisting of either pulses of cyclophosphamide every 3 months, or, preferably, daily MMF or daily azathioprine. This maintenance therapy would be continued for approximately 2 years.

If the disease is less threatening, or if the patient or physician is hesitant to use cyclophosphamide or would prefer MMF, induction with MMF is a very reasonable alternative (as shown in Option 5). The dose of MMF would be 500 mg twice daily for 1 week, then 750 mg twice daily for 1 week, then 1000 mg twice daily for 1 week, with plans to increase at weekly intervals to a maximum dose of 1000 mg three times daily. If the patient’s situation is more urgent, the MMF can be started at a higher dose and/or advanced much more quickly. MMF would then be continued, as maintenance therapy, for a total of 2.5 years. Another alternative would be to give 3 initial pulses of CTX, and then switch to MMF.

For patients with extremely severe disease, or disease that is not seeming to respond adequately to the above “induction” therapies, it would be reasonable to consider adding rituximab or infliximab. Another consideration for very severe disease is plasma exchange. When rituximab or infliximab are added, it might be possible to provide less exposure to corticosteroid than is depicted in Options 10 and 11.

We would consider adding oral, subcutaneous, or IV methotrexate (15–20 mg weekly) to MMF when MMF is used for induction or maintenance.

An alternative to MMF would be Azathioprine. (In many countries, MMF is either not available, or is too expensive.) It is quite possible that azathioprine is not as effective as MMF, but this is unclear.

Other alternatives to MMF would be cyclosporine A and tacrolimus (one or the other). For particularly severe disease another consideration would be a combination of MMF plus tacrolimus (based on experience with this combination in treatment of lupus).
It is probably wise for all patients to be treated with daily low-dose aspirin (81 mg/d).

Although some have suggested treatment with anticoagulants, we do not recommend anticoagulation. We also do not recommend treatment with a vasodilator.

**Prednisone tapering**

The “conventional” prednisone tapering schedule mentioned earlier is only a guideline. Tapering should be continued only if the patient is tolerating each step. The tapering pace can be speeded up for patients with less severe disease, or disease that is improving more rapidly than usual. Patients with more worrisome disease can be kept on 60 to 80 mg/d throughout the first 6 weeks and then tapered slowly, weekly, over the next few weeks until their tapering pace catches up with the “conventional tapering” schedule. Again, the pace of tapering depends on what other immunosuppressive therapies are being used.

The conventional prednisone tapering schedule (e.g. the tapering shown in Options 1, 4-6) typically works very well for patients whose disease follows a monophasic course. The tapering pace is designed to be just slightly slower than the usual pace of self-correction that occurs with monophasic autoimmune disease.

When a patient responds well to initial therapy but eventually fails to tolerate the conventional prednisone tapering schedule, that failure is usually due to one of the following:

- The pace at which the patient’s monophasic disease is self-correcting is slower than the pace of prednisone tapering. In such an instance, it will be necessary to go back to dosage levels that were working well, and then taper more slowly.
- The patient is having a spontaneous relapse—i.e. the disease is following a fluctuating monophasic course, and disease intensity has spontaneously increased. In such an instance, it will be necessary to escalate treatment, often considerably. For example, it may be necessary to again give three consecutive daily pulses of methylprednisolone, perhaps followed by weekly pulses, and it may be necessary to go back to 60 mg of oral prednisone, with plans to taper as quickly as clinical conditions permit. If the patient has been off IVIG, it may be wise to resume it at 2 g/kg/mo. If the patient has not yet received IVIG, MMF or Cyclophosphamide when the relapse occurs, the addition of IVIG and either MMF or cyclophosphamide should be considered. Addition of rituximab or infliximab is also a consideration.
- The patient’s disease is following a prolonged, chronic, continuous course (because of relatively poor capacity for immunologic self-correction). In this case, further conventional tapering will result in further worsening of disease. Go back to the drugs and dosages that were last working well and stay on that treatment for a fairly long time, with only slow tapering. If the patient has not yet been started on IVIG, MMF, or Cyclophosphamide, consider adding IVIG and one of the other two. If worsening has occurred despite maximum conventional immunosuppression, alternative medications will need to be considered, such as cyclosporine A, tacrolimus, rituximab, or infliximab.

Instead of using conventional high-dose oral prednisone (and conventional tapering) for initial treatment and/or treatment of relapses, an alternative is an extended course of frequent pulses of methylprednisolone (with lower doses of prednisone), as depicted in Options 7-12.
Other Medications and Treatments

The use of rituximab, Infliximab, and plasma exchange for SS have been studied on only a very limited and anecdotal basis. If further studies reveal promising results, rituximab or infliximab might become a good options, not only for patients who fail to respond to conventional treatment, but also for initial treatment (instead of Cyclophosphamide or MMF and such extensive exposure to corticosteroid, or even with Cyclophosphamide or MMF) and for relapses.

Tacrolimus and cyclosporine A have not been studied in Susac’s syndrome, but represent additional options.

Interferons are not effective in SS. We are aware of several patients do poorly after being placed on interferon therapy when their SS was misdiagnosed as multiple sclerosis.

Summarizing comments regarding the 11 Treatment Options

- Option 1:
  - This is a standard plan for treatment (during the first year) of any severe organ-threatening or life-threatening autoimmune disease (e.g. severe lupus nephritis, severe dermatomyositis, or severe encephalopathic Susac’s syndrome).
  - Three (or more) initial pulses of methylprednisolone (1 gm/dose, on 3 consecutive days).
  - Initial high dose oral prednisone (20 mg TID for 2 weeks, then 30 mg BID for 2 weeks), with subsequent conventional tapering (using a QAM dose).
  - Monthly infusions of IVIG for at least 6 months.
  - Monthly pulses of IV cyclophosphamide 500-750 mg/M2 Q month x 3-7, followed by maintenance therapy with mycophenolate mofetil (MMF).

- Option 2:
  - This is the same as Option 1, but with a more rapid prednisone taper (designed to minimize potential prednisone side effects).

- Option 3:
  - This is the same as Option 2, but with provision of monthly pulses of methylprednisolone (to protect against the possibility that the more rapid prednisone tapering might be too rapid)

- Option 4:
  - Same as Option 1, except for quicker conversion from cyclophosphamide to mycophenolate (designed to minimize exposure to cyclophosphamide).

- Option 5:
  - Same as Option 1, except for use of mycophenolate from the very beginning, instead of cyclophosphamide. Similarly, it would be very reasonable to use MMF from the very beginning (and not use any cyclophosphamide) in Options 1-4 and 7-13

- Option 6:
  - Same as Option 5, except for addition of Methotrexate (MTX) to the mycophenolate, from the beginning. (The combination of MTX plus mycophenolate might provide better immunosuppression than mycophenolate alone, without much increase in side effect potential)

- Option 7:
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- Same as Option 1, but with reliance on frequent pulses of methylprednisolone, and less reliance on oral prednisone.
- The frequent pulses of methylprednisolone permit a more rapid tapering of oral prednisone.
- The number of consecutive weeks during which the patient receives 3 pulses/week, 2 pulses/week, or one pulse/week is flexible (i.e. should be adjusted according to the patient’s response/needs) and can be more or less than that shown.

- Option 8:
  - Same as Option 7, but with quicker conversion from cyclophosphamide to mycophenolate.

- Option 9:
  - Same as Option 7, but with even more rapid tapering of prednisone.

- Option 10:
  - This (and Options 11 and 12) is a good option for the most severe/threatening cases of Susac’s syndrome.
  - The use of rituximab might permit a quicker conversion to mycophenolate, as well as more rapid tapering of oral prednisone.
  - The use of frequent pulses of methylprednisolone permits more rapid tapering of oral prednisone (and, thereby, fewer steroid side effects).
  - NOTE: For Options 10-12 (and 1-4 and 7-9, for that matter), MMF could be used from the very beginning, instead of using any cyclophosphamide.

- Option 11:
  - This is the same as Option 10, except that infliximab is used instead of rituximab.

- Option 12:
  - This is the same as Option 10, except that plasma exchange is used instead of rituximab.

- Option 13:
  - This is the same as Option 4, but allows for a slower prednisone tapering schedule.

Treatment of the BRAO/HL Course Subset

Because the consequences of under-treated BRAO/HL are usually not as devastating as those of under-treated encephalopathy, it is possible that treatment of BRAO/HL may not need to be as aggressive or as prolonged as treatment of encephalopathic SS. On the other hand, when a patient presents with a first episode of nonencephalopathic BRAO/HL it is impossible to predict if or when encephalopathy is likely to occur. Because of this unpredictability, we advise aggressive treatment of initial episodes of non-encephalopathic BRAO/HL, using the previously described recommendations.

What about patients who clearly belong to the Recurrent BRAO/HL group?

- Should these patients be treated differently than the typical encephalopathic patient? Probably so.
- Should they be treated only episodically---i.e. prn, each episode at a time, with minimal or no treatment between episodes? Maybe. It depends on how frequently the episodes are occurring, how threatening the episodes are, and how much risk taking the patient and physician are comfortable with.
For example, an individual episode could be treated with either 3 pulses of IVMP or a brief course of high dose prednisone (60 mg per day for one week, with tapering over one month, or less) and IVIG (x 1-2, or until the episode has clearly remitted), with no plans to treat between episodes. This would be reasonable for a patient who has clearly shown a well-established pattern of BRAO/HL and is by now having only 1-2 episodes (or fewer) per year. If this plan is adopted, however, frequent FA studies would be wise to detect any subclinical active disease between episodes.

Or, should they be treated both episodically (as above), but also be placed on a "preventative" immunosuppressive drug (like mycophenolate mofetil and/or scheduled Q 1-2 month IVIG) for a year or two, or more?

This would seem wise early in the course of BRAO/HL because early in the course it is unpredictable how frequent the episodes will be and it is unpredictable whether CNS involvement is just around the corner or will never occur.

Then, once the patient has shown that they are fairly predictably having only 1-2 episodes per year (or fewer) and no hints of encephalopathy, one could consider prn therapy.

We have found regular use of IVIG (Q1-3 months for 1-2 years, or longer) to be particularly helpful for patients with mild-moderate versions of the recurrent BRAO subset---even as a monotherapy (or in combination with MMF).

Is rituximab warranted for these patients? This probably depends on:
- How frequent the episodes are,
- How threatening the episodes are (to vision and to hearing)
- How certain we can feel that CNS involvement is not occurring, or not likely to occur in the near future.
- How abnormal the MRI is.

We would strongly consider rituximab if:
- There were any hints of potentially threatening CNS disease
- If the retinal disease was frequently active and we were worried about possible accompanying subclinical CNS disease.
- If the MRI shows more than mild abnormalities.

How should these patients be followed?
- Frequent FA would seem wise---Q 1-2 months initially, then Q 3-4 months until stable, then Q 6 months x 2-3, then Q year x 3, then prn.
- Serial audiograms---perhaps a similar schedule.
- Serial MRIs Q 6 month x 4, then Q year x 4, at least.
- Serial formal neuropsychology testing; Q 6 months x 2, then Q yearly x 6, at least.

**Long-Term Management**

The most challenging aspect of SS treatment is long-term management. The natural history of an individual patient’s SS is difficult to predict and discern, at least initially. It is not easy to determine when it is safe to start tapering medication, and at what pace. Relapse is common when therapy is tapered too quickly. It is
often difficult to recognize exacerbation early in its course or to decide how much escalation of therapy is needed for a given exacerbation.

Serial ophthalmologic, audiologic, neuropsychiatric, MRI, and laboratory evaluations can provide important guidance. Serial fluorescein angiography (FA) may be the most sensitive way to detect early, active, subclinical, pre-occlusive endotheliopathy (as evidenced by fluorescein leakage), at least in the retina (and perhaps also in the brain or inner ear). For this reason it is wise to consult, early on, an ophthalmologist who has particular expertise in interpretation of FA—usually a retinal specialist. We also advocate serial use of disease assessment tools, such as the SS-Disease Activity Score (SS-DAS) so that the physician, patient, and family can carefully keep track of the patients ongoing progress.

**Weighing Risks versus Benefits of Treatments: An Approach to Making Difficult Treatment Decisions**

Physicians and patients/families very often need to choose between two (or more) treatment options, each of which involves risks. For example, in the case of a patient with a severe encephalopathic form of SS, option A might be to rely on corticosteroid and IVIG (without cyclophosphamide or mycophenolate mofetil); option B might be to add cyclophosphamide or MMF (to corticosteroid and IVIG); With option B there is worry about potential side effects of cyclophosphamide or mycophenolate mofetil (in that order of worry). But, with option A there is worry that this treatment might fail to adequately control the disease, resulting in potentially serious and regrettable “side effects” from the disease. How does a physician, patient, or family member decide between these options, when there are legitimate and serious worries associated with each?

One approach is to make the choice by asking the question: “Which decision (going with option A or B) am I least likely to regret at sometime in the future?” In other words, “What is the likelihood that I will end up regretting that we chose option A? What is the likelihood that I will end up regretting that we chose option B? And, how do these three likelihoods compare?

What is the likelihood of eventually regretting a decision to proceed with option A?

- This decision would prove to be regrettable if the patient ended up with severe complications of the disease—particularly severe cognitive impairment, but also severe hearing impairment, or severe visual impairment.
- Unfortunately, when severe encephalopathic SS is treated with only corticosteroid and IVIG, the likelihood of severe encephalopathic SS resulting in a regrettable degree of irreversible cognitive dysfunction is not small. It is an appropriate and big worry.
- In other words, it is not hard to imagine eventually regretting a choice to go with option A.
- Therefore, the likelihood of eventually regretting a decision to go with option A is not small.

What is the likelihood of eventually regretting a decision to proceed with option B?

- Option B (addition of cyclophosphamide or MMF) would give considerably more protection against the potential “side effects” of the disease, than would treatment with corticosteroid and IVIG alone. That is, it is more likely that the patient would avoid regrettable disease complications if cyclophosphamide or MMF is part of the initial treatment.
- A decision to go with option B would eventually prove to be regrettable, if the patient ultimately developed hemorrhagic cystitis, or bladder cancer, or sterility as a result of cyclophosphamide therapy.
- However, although these potential side effects of cyclophosphamide are quite worrisome, it is, in reality, statistically unlikely that the first two regrettable side effects from cyclophosphamide would
actually occur (with IV pulse cyclophosphamide), and the possibility of sterility may be of relatively less concern than the possibility of permanent injury from the disease itself. MMF involves less side effect risk than does cyclophosphamide.

- So, the over-all likelihood of eventually regretting a decision to go with option B, is not minimal, but is relatively small.

When we compare the likelihood of eventually regretting option B to the likelihood of eventually regretting option A, which likelihood worries us the most?

- The likelihood of regretting option A is: Not small.
- The likelihood of regretting option B is: Relatively small.
- In other words, the likelihood of eventually regretting options A would seem greater than the likelihood of eventually regretting option B. Options A would seem to have greater worries associated with it, overall, than option B—particularly if MMF is chosen over cyclophosphamide.

It seems more likely that we might end up regretting the choice of option A than B. It makes greatest sense to choose the option that has fewer overall worries associated with it and is least likely to result in eventual regret.

Therefore, option B seems better than A for severe encephalopathic SS.

So, in addition to thinking about the short term, it is important to think about the potential long term consequences of a decision. In the short term, Option A may seem more appealing, while Option B seems more worrisome. But, if we look beyond the short term and anticipate how we might feel months or years from now about a decision we make now—Options A appears to be more risky, more worrisome, and less appealing than Option B.

The same thought process may be applied to decisions about whether to add infliximab, rituximab, or plasma exchange.