A diagnosis of Sjögren’s syndrome does not automatically mean that treatment is necessary. Once a diagnosis of Sjögren’s syndrome has been made, an assessment is necessary of any damage and what developments may be expected in the future.

The possibility and need for treatment depend on the signs, symptoms and risks of the disease. Possibilities for treating Sjögren’s syndrome are not different to those for other generalized autoimmune diseases. Due to the wide variation in signs and symptoms, treatment may greatly differ per patient, while considerable individual variations are also seen in the effect of medication on the patient. Sjögren’s patients have an increased risk of allergic reactions to drugs.\textsuperscript{1,2}

After the assessment, the following scenarios for treatment are possible:

a. treatment is necessary for medical reasons
b. the patient wishes to have treatment for a specific symptom
c. treatment is neither necessary nor desired.

The advantage of this approach is that it is clear why treatment is being given, how the result is evaluated and whether the treatment should be continued or stopped after a specific period of time. Indications for treatment can be subdivided into inflammation, dryness and other indications.

**Has the desired effect of a drug been obtained?**

When a drug is being taken, it is important to assess after a period of time whether the desired effect has been achieved.

Laboratory tests can be used to evaluate objective signs of the disease, such as inflammation.

Assessment of the effect of a drug on symptoms is dependent on the patient’s own impression.

If after a period of time no improvement is seen in signs or symptoms, there is no point in continuing with the drug in question. When assessing symptoms and signs, account should be taken of their natural course.

This is difficult if the signs or symptoms are subject to remissions and relapses and consequently very variable. This is explained in figure 5.1. Let us assume that a symptom has a natural course as shown by line a. If a treatment is started at time 1 and the sign or symptom improves as shown by line b, the drug has an unmistakeably positive effect, but despite this the sign or symptom has become worse.

Suppose that the sign or symptom has a natural course as shown by line c. A treatment is started at time 2. Here, the sign or symptom decreases in all cases, for example if the drug has no effect (d), a positive effect (e) or even a negative effect (f).

The conclusion is therefore that a longer period of time is usually necessary to assess whether a drug has had a positive effect. A critical approach and common sense help accurate assessment of any effect.

This chapter on treatment is divided into a section on treatment of symptoms and signs and a section on specific drugs.
A. TREATMENT FOR SPECIFIC SYMPTOMS OR SIGNS

This section is divided in treatment of dryness, inflammation and for disease manifestations that cannot be classified as dryness or inflammation.

TREATMENT OF DRYNESS

Sjögren’s syndrome is first and foremost an exocrinopathy, an abnormality of exocrine glands (glands that secrete moisture). This may cause severe symptoms. By definition this concerns the eyes and mouth, but the dryness may also occur in other organs such as the nose, bronchial tubes, vagina, skin and intestines.

In some organs symptoms of dryness can be treated locally, e.g. the eyes (artificial tears), the mouth (artificial saliva), the nose (ointment) and the skin (cream). Local treatment may be sufficiently effective, particularly in the case of mild symptoms.

Disadvantages, however, are that they only have a local effect and are not really an adequate replacement for your own tears, saliva etc.

Systemic treatment (use of medication for a general effect, e.g. by taking tablets) is gaining increasing importance in the treatment of dryness. Advantages are that it stimulates the formation of your own moisture, including the protective substances they contain, and that it is often effective in more than one part of the body. Disadvantages are that these are drugs that may have side-effects and are not effective and/or suitable for everyone. The main drugs used for systemic treatment are pilocarpine 3-5 (see paragraph on pilocarpine) and cevimeline 6,7 (not obtainable in Europe). Positive effects can also be seen from bromhexine 3x 8-16 mg/day,8-10 N-acetylcysteine 3x 200 mg/day 11 or nizatidine 300 mg/day.128,129 If required, pilocarpine can be combined with each of them. Treatment with pilocarpine and nizatidine will be discussed further.

In a prospective, randomized, double-masked trial, omega-3 was not found to be better than wheat germ oil in stimulating saliva production.166

Local treatments of dryness

Local treatment of dry eyes

In many patients, eye irritation can be improved with artificial tears, preferably no more than 4-6x a day. If the result is unsatisfactory, it may be worthwhile trying another brand (see also chapter 20, question 45).

Some people are unable to tolerate certain preservatives that are added to bottles of artificial tears. It is then worth trying artificial tears containing a different preservative or trying preservative-free artificial tears. These are often supplied in single use containers or a special bottle which can be used for up to three months once opened.

Local treatment of dry mouth

Artificial saliva products, such as Xialine* and Saliva orthana®, are available for local treatment of the mouth. Glandosane* is a watery artificial saliva that is effective for a short period of time. Oral Balance® is a gel that is mainly suitable at night. The effect of these treatments depends on the correct usage, so read the instructions for use carefully.

A disadvantage is that artificial saliva cannot be used for eating problems. Dryness of the mouth can cause gumline caries around the neck of a tooth. It is important to discuss the use of e.g. fluoride tablets and/or application of fluoride with your dentist and have frequent check-ups, for example every 3 months.

Local treatment of dry nose

Symptoms caused by dry mucous membranes in the nose can be treated locally using physiological salt. If there is crust formation in the nostrils, an ointment containing 10% Emser salt in oculentum simplex or Nisita® nose ointment can be used. You can make physiological salt (0.9%) yourself by dissolving 9 grams of kitchen salt (NaCl) in 1 litre of water. Place a little of this solution in the palm of your hand and sniff it hard up into your nostrils. You should spit out any water that runs down into your throat. Do this several times consecutively and repeat it a couple of times a day.

Local treatment of dry skin

Many patients with Sjögren’s syndrome have a dry skin. Showering should be short and the water not too hot. After showering, smear your skin while still wet with 20% vaselinum album in cremor lanette I. Allow this to sink into your skin for a few minutes before dressing.

Local treatment of dry vagina

Dryness of the mucous membranes of the vagina can have different causes, such as the menopause, but is also a well-known symptom of Sjögren’s syndrome.

Treatment with pilocarpine (see further) improves (symptoms of) vaginal dryness in about one-third of women. Lubricants (e.g. Sensilube®, KY Jelly®) can be used if required. The following alternative can be made up on prescription by the pharmacy:

- hypromellose 3 gr
- glycerol 85% 50 gr
- methylparabene 15% FNA 1 ml
- water to make a total of 100 ml
TREATMENT OF INFLAMMATION
Inflammation in Sjögren’s syndrome is caused by the infiltration of organs by mainly CD4+ T lymphocytes. These organs are the lacrimal glands (resulting in keratoconjunctivitis sicca) and the salivary glands (focal lymphocytic sialoadenitis). Similar inflammation may occur in the bronchial tubes (bronchitis sicca), lungs (lymphocytic interstitial pneumonia), kidney tubules (interstitial nephritis), stomach (autoimmune gastritis) and liver (autoimmune hepatitis and primary biliary cirrhosis). Inflammation may also occur in the small blood vessels (leukocytoclastic vasculitis) and joints (arthritis). Vasculitis can damage organs due to impaired blood circulation.

Inflammation should be treated if it is likely to cause damage to an organ. If this is only expected in the longer term, the patient can be treated with hydroxychloroquine (HCQ), usually 400 mg/day for 3 months, followed by 200 mg/day (see also section on HCQ). If there is a risk of organ damage in the short term, temporary treatment with corticosteroids may be necessary, preferably in combination with HCQ. After a few months, the treatment with corticosteroids can be stopped again. In the case of inflammation that is unlikely to lead to damage but which nevertheless requires treatment of the symptoms it causes, NSAIDs (prostaglandin synthesis inhibitors) can be used for a period of time. The principle behind treatment with HCQ, corticosteroids and NSAIDs is explained in figure 5.2 (see text accompanying the figure).

Inflammation of the tear glands and ocular surface
Tear glands
Inflammation of the lacrimal glands does not usually necessitate separate treatment. If required, the above-mentioned agents can be used.

Ocular surface
If the surface of the eyes is inflamed, treatment with the usual artificial tears can be supplemented by eye-drops containing an anti-inflammatory agent such as cyclosporine A 0.05% (Restasis®) 2-4 times a day or corticosteroid, or with autologous serum.

Topical corticosteroid is effective in achieving rapid resolution of acute inflammation, whereas topical cyclosporin A would be safer for long-term maintenance. These anti-inflammatory therapies provided subjective improvement in dry eye symptoms in 70% of patients.

Eye drops containing vitamin A as retinyl palmitate have been found to be equally effective as cyclosporin A 0.05% in patients with dry eye syndrome. Note: dry eye syndrome is a general term for various disorders attributable to tear deficiency or excessive evaporation that causes damage to the interpalpebral ocular surface and is associated with symptoms of discomfort.

Vitamin A
Vitamin A is essential for maintaining the health of epithelial cells. Vitamin A deficiency adversely affects these cells in the eyelid, conjunctiva, and cornea. Vitamin A can exist in 3 forms: retinol, retinal, and retinoic acid. Many tissues requiring vitamin A store the vitamin as an ester of retinol. Retinyl palmitate (an ester of retinol and palmitate) is found in cells of the lacrimal gland and retinol is found in the tears. Its presence in tears provides the rationale for treating dry eye disease with vitamin A.

Figure 5.2 Graph illustrating the principle of treating inflammatory conditions with hydroxychloroquine, corticosteroids and NSAIDs. The red line A shows the variable course of the disease activity over a number of years and line B the average disease activity. The purpose of hydroxychloroquine is to (gradually) reduce the disease activity as illustrated by the downward trend of lines A and B over the years. Non-dangerous flare-ups of the disease (C) can be successfully treated with NSAIDs on a temporary basis. Dangerous flare-ups (D) should be treated with short courses of corticosteroids.

Disease activity and disease damage
The course of many autoimmune diseases is characterized by periods of disease inactivity and disease activity (flares). Flares show variable resolutions or persist resulting in damage to the affected organ. It is very important to distinguish disease activity from damage as activity may be reversible while damage may be permanent (irreversible). See chapter 17 for further information.
Inflammation of the mouth

Infection with Candida albicans can cause a burning, red tongue and cracks in the corners of the mouth.\textsuperscript{12-14} Topical treatment is possible with amphotericin B (Fungizone\textsuperscript{®}) in many patients as long as some saliva is produced. Systemic treatment with tablets often works better than local treatment, for example 200 mg fluconazole for 15–30 days. If the fungal infection returns after this, treatment with \textit{e.g.} 50 mg fluconazole a day may be necessary for 3 months. Another agent can also be tried, for example itraconazole, 2x 100 mg/day for 30 days. Sometimes the fungal infection is resistant to both of these agents. If this is the case, a combination of 200 mg fluconazole and 250 mg terbinafine for 14 days is often a solution.\textsuperscript{15}

If symptoms recur, treatment with fluconazole 150 mg once a week may be effective in preventing symptomatic oral candidiasis (see also reference 76). Take a new toothbrush and disinfect any dentures.

In a study in which patients with Sjögren’s syndrome were treated with 3x 5 mg/day pilocarpine, at the start of the study 75% of the patients were found to be infected with \textit{Candida albicans}. After a year’s treatment, this percentage had fallen to 25%.\textsuperscript{16}

Inflammation of the salivary glands

About a third of patients with Sjögren’s syndrome experience unilateral or bilateral swelling of the large salivary glands.\textsuperscript{17,18}

The swelling may sometimes be bothersome or painful and require treatment. It should be borne in mind that infections, stones and malignancies can sometimes be a cause of swelling. If this is not the case, good results can be achieved by using HCQ with pilocarpine and/or bromhexine.\textsuperscript{19,20}

In rare cases, a short treatment (\textit{e.g.} 1-2 weeks) with corticosteroids can be beneficial. If the swelling forms a constant and/or recurrent problem and if there is an increased risk of a non-Hodgkin lymphoma (high sedimentation rate, antibodies to SSA/Ro and/or SSB/La, monoclonal or oligoclonal abnormalities), it may be necessary to remove the salivary gland surgically (see also the chapter on surgery and anaesthesia for special precautions to be taken in the case of operations).

Acute parotid swelling

Acute parotid swelling is usually due to bacterial infection of the parotid gland and a common complication in patients with Sjögren’s syndrome. It may be effectively treated with 500 mg of levofloxacin once daily for 30 days.

Acute bacterial infection of the parotid gland, a common complication in patients with Sjögren’s syndrome, may be effectively treated with 500 mg of levofloxacin once daily for 30 days.

Inflammation of muscles and joints

When considering whether to start treatment for arthritis, it should be remembered that joints are virtually never damaged by Sjögren’s syndrome alone. If a second autoimmune disease is present, it should be investigated whether the arthritis is related to this. Generally speaking, arthritis resulting from rheumatoid arthritis will be treated to prevent damage to the joints.

Muscle inflammation (myositis) is relatively rare and mild forms either require no treatment or can be treated with hydroxychloroquine.\textsuperscript{21} The indication for treating inflammation of joints and muscles in Sjögren’s syndrome is therefore mainly the accompanying pain (see under: Pain in muscles and joints).

Inflammation of the lungs

The branches of the windpipe, the bronchi or bronchial tubes, may become inflamed due to dryness. This is known as bronchitis sicca \textsuperscript{22-24} and can be improved by the use of pilocarpine with or without bromhexine or acetylcysteine.

The lungs may contain lymphocytic infiltrates, comparable with those found in the salivary and lacrimal glands.\textsuperscript{25,26} This condition is known as lymphocytic interstitial pneumonia for which treatment with prednisolone is usually necessary, sometimes with the addition of azathioprine. Mild forms sometimes respond well to HCQ. Active forms of this inflammatory condition sometimes lead to a non-Hodgkin lymphoma in the lungs.\textsuperscript{27-30} Pulmonary disorders in Sjögren’s syndrome are discussed in a separate chapter.

Inflammation of the skin

Skin complaints caused by exposure to sunlight can often be treated with HCQ 200 mg/day.\textsuperscript{31,32} However, HCQ can sometimes make the skin more sensitive to sunburn and invariably exacerbates pre-existing or subclinical psoriasis.\textsuperscript{33-39}

Inflammation of blood vessels (vasculitis)

Vasculitis (inflammation of the blood vessels) occurs in a quarter of patients with Sjögren’s syndrome, usually in the form of hypersensitivity vasculitis (leukocytoclastic vasculitis) with for example hives (urticaria) or purpura (dot-like bleeding into the skin), particularly on the lower legs. In rare instances, medium-sized blood vessels (arteries) are involved in the process. As in other complications, the need for
treatment and the method to be used depends on the degree or risk of organ damage. This treatment can vary from prostaglandin synthesis inhibitors (NSAIDs), non-NSAIDS (e.g. HCQ, colchicine, diaphenylsulfone (Dapsone®) to corticosteroids and drugs such as azathioprine. An even more aggressive therapy, e.g. cyclophosphamide, may be necessary in the case of vasculitis of the central nervous system or in polyarteritis nodosa forms of arteritis (inflammation of medium-sized arteries).

**Inflammation of the kidneys**

At least three different kidney disorders may occur in Sjögren’s syndrome. 

*Interstitial nephritis* (inflammation of the renal tubules) may diminish the kidney function in some patients. Treatment is given then with prednisolone. If the kidney function (creatinine clearance) is normal, treatment may only be necessary for any associated acidosis, hypokalaemia (low potassium in the blood) or hyperventilation.

*Glomerulonephritis* (kidney filter inflammation) is rare in Sjögren’s syndrome, in contrast with systemic lupus erythematosus (SLE). Treatment with corticosteroids and e.g. azathioprine, cyclophosphamide or a mycophenolate is usually necessary.

A third kidney problem can occur as a manifestation of the antiphospholipid syndrome (APS), when small clots or thrombi occur in the blood vessels causing insufficient blood flow to the kidney. Treatment consists of anticoagulation.

**Nonbacterial inflammation of the urinary bladder**

Interstitial cystitis (bladder pain syndrome) is a nonbacterial inflammatory condition of the urinary bladder. It was recently found that interstitial cystitis is not uncommonly associated with either Sjögren’s syndrome or individual components such as keratoconjunctivitis sicca or focal lymphocytic sialoadenitis. For further information see the chapter on urogenital disorders.

**VARIOUS DISORDERS**

Some features of Sjögren’s syndrome cannot be classified as inflammation or dryness. These include: thrombocytopenia, antiphospholipid syndrome, hypergammaglobulinaemia, cryoglobulinaemia and Raynaud phenomenon. Treatment corresponds to that for the isolated forms and for other autoimmune diseases. They are briefly discussed below.

**Thrombopenia and antiphospholipid syndrome**

Thrombopenia (low platelet count) occurs in about 11% of patients with Sjögren’s syndrome and only needs treating in the case of (a risk of) haemorrhaging. In the first instance this consists of a high dose of corticosteroids. If necessary, gammaglobulins (IgG) can also be administered intravenously. If this proves inadequate, removal of the spleen may be considered. A new approach is the anti-B cell therapy with e.g. rituximab (see further). Severe autoimmune thrombopenia rarely occurs with Sjögren’s syndrome and may be a reason to suspect SLE.

Thrombopenia may also be associated with antiphospholipid antibodies in APS. APS may also manifest itself in the form of recurrent thrombosis in veins or arteries (lung embolism, cerebral thrombosis, aseptic bone necrosis) and repeated miscarriage. This form of thrombopenia may respond well to salicylates (aspirin), e.g. between 38 and 120 mg calcium carbasalate a day, although this treatment cannot be started in a period when there is a strong tendency to bleed.

**Raynaud phenomenon**

Raynaud phenomenon occurs in about one third of patients with Sjögren’s syndrome. It is important to test for cryoglobulinaemia (see box) or other causes of increased viscosity (stickiness) of the blood (such as a greatly increased IgM level) that need to be treated separately (see chapter 14).

It is essential to keep the whole body warm, including the (fore)head. Smoking is strictly advised against. Drugs can sometimes lead to an improvement, with the possibility of treatment in the winter only. A Cochrane review showed that calcium channel antagonists (e.g. sustained-release nifedipine 2-3x 10-60 mg/day) were the only group of drugs with proven efficacy in Raynaud phenomenon. The treatment sometimes has to be stopped due to headache or low blood pressure. Other possible drugs that are used but with less well documented efficacy are ketanserin (1-3x 20-40 mg/day) and fluoxetine (20 mg/day).

If ulcers develop on the hands or feet, 38-100 mg/day calcium carbasalate may help to speed healing and prevent new ulcers.

**Sympathectomy (cutting through specific nerves)** is not recommended for Raynaud phenomenon.
**Cryoglobulins**

Cryoglobulins are complexes of mainly antibodies that form a gel at low temperatures and can consequently make the blood ‘thicker’. They mainly occur in malignant blood diseases, autoimmune diseases (especially Sjögren’s syndrome) and in infection with the hepatitis B or hepatitis C virus. Cryoglobulinaemia means the occurrence of cryoglobulins in the blood.

**Hypergammaglobulinaemia and cryoglobulinaemia**

In some patients, the concentration of the serum immunoglobulins (antibodies) is increased (hypergammaglobulinaemia).

Greatly increased concentrations of IgG and IgM, with or without cryoglobulins, can cause vasculitis and hyperviscosity (blood is too thick and sticky). If tests show that the IgG and/or IgM levels are continually increasing, it is useful to start early treatment with HCQ. This will allow the levels to stabilize and then decrease. If problems already exist due to high concentrations of immunoglobulins, treatment may be necessary with corticosteroids and immunosuppressive agents. This also applies to severe forms of cryoglobulinaemia (see chapter on clinical investigations).

**SUBJECTIVE INDICATIONS FOR TREATMENT**

Patients often have symptoms for which there is no medical need for treatment. If these symptoms have a very detrimental impact on the patient’s quality of life, the advantages of treatment may be greater than the disadvantages. This may be the case for example with (debilitating) fatigue and severe muscle and joint pain, with or without objective signs of inflammation.

**Fatigue**

Fatigue is an important, frequently occurring symptom in Sjögren’s syndrome and often forms a particularly debilitating aspect of the disease for the patient. It can come on quite suddenly and greatly vary per day. Since fatigue cannot be seen and is difficult to assess objectively, it often causes major problems for the patient at work and within the family.

Furthermore, medical examining authorities often have little or no conception of fatigue as such. See the chapter on fatigue.

It is first necessary to investigate whether there is any specific identifiable cause of the fatigue, either in relation to the Sjögren’s syndrome or some other cause. If a cause is found, this can often be treated successfully and the fatigue may subside.

If inflammation in the joints, muscles or blood vessels is the cause of the fatigue, anti-inflammatory agents such as HCQ, NSAIDs and prednisolone can be used for treatment. Prednisolone has, not without reason, acquired a somewhat tarnished reputation among both doctors and patients. However, one should be aware of “throwing out the baby with the bath water”. Provided that there is a good reason for it, low doses of prednisolone taken for several weeks and preferably on alternate days can some times lead to a substantial improvement without giving rise to side effects. If necessary, this can be repeated several times a year.

If sleep disturbance due to insufficient sleep at night is the cause of the fatigue, this should be treated by trying to eliminate the cause. This might be pain or anxiety, for example.

Depression is a common cause of tiredness. However, the drugs used to treat this often exacerbate the dryness symptoms of the mouth and eyes.

If a patient has DRTA (distal renal tubular acidosi), referred to earlier, potassium citrate, e.g. 3x per day 0.5 to 2 grams, can help to restore the acidity level and to correct the lower than normal serum potassium. It is very important for the potassium level in the blood to be regularly checked since potassium levels that are too high are dangerous. If there is no need to correct the potassium level, sodium citrate or magnesium citrate can be used as well in equivalent dosages.

If the magnesium in the red blood cells is too low, magnesium gluconate helps (3x two capsules of 250 mg). These forms of treatment are safe provided they take place under medical supervision.

If the fatigue is severe, it may be worth considering trying to improve it with certain drugs (e.g. HCQ or rituximab). This is only justifiable if the balance between the possible side effects of the drug and the result that can be expected is favourable.

A small double blind placebo-controlled study has shown that two infusions of rituximab 1 gr (with oral and intravenous steroids to avoid serum sickness) significantly improvement fatigue and social functioning six months later. See further for more information on rituximab.

If treatment is not possible or unsuccessful, the only possibility that remains is to adapt one’s life style. A few rules of thumb may help here:

- get up on time because lying in bed too long can exacerbate the fatigue (maintain a normal day and night rhythm)
- divide up your day, start by doing something for a couple of hours and then rest for about 20 minutes
- you may need 3 to 4 rest breaks during the day
- avoid stress peaks by spreading activities throughout the day and week
- try to prioritize by using your energy on activities that you yourself find important and not on what you feel others expect you to do (be a bit “egoistic”).

**Pain in muscles and joints**

If treatment is required for pain in the muscles and joints, the first choice after paracetamol (acetaminophen) would be HCQ, followed by prostaglandin synthesis inhibitors (preferably the lowest effective dose of selective cox-2 inhibitors such as celecoxib or etoricoxib, see further). The same applies to inflammation of muscles and joints (see above), but paracetamol will only have a pain relieving effect.

The preference for HCQ is connected with the relatively infrequent occurrence of side effects and the fact that it is often an effective treatment for more than one problem.

HCQ can be effective for skin disorders caused by sunlight (increased sensitivity to sunlight is a rare side effect), for treating signs and symptoms of leukocytoclastic vasculitis in the skin, for (poly)myositis, it reduces the risk of thrombosis by antiphospholipid antibodies and lowers a high IgG level. The results achieved from treating joint and muscle pain differ greatly per patient and per drug.

**Depression**

Depression is not uncommon in Sjögren’s syndrome. The depression may be a reaction to having the disease and is often of a temporary nature.

Fatigue (especially fatigue that is present first thing in the morning and improves during the course of the day), difficulty concentrating, forgetfulness, poor appetite and sleep disturbances may be symptoms of depression. Bearing in mind that vasculitis, particularly of the small blood vessels, can cause neuropsychiatric symptoms, it is worthwhile treating any existing vasculitis (see above) if there are indications that the depression could have an organic cause. Tests should also be carried out to check for antiphospholipid antibodies in the blood because these can cause thrombosis, including in small blood vessels in the brain. Recurrent minor damage can eventually lead to severe disorders.

If the depression has no organic cause, help is needed from a psychotherapist. When treating, it is important to use modern antidepressants without an anticholinergic side effect that might otherwise considerably exacerbate the symptoms of dryness. The term “anticholinergic side effect” means that the drug inhibits certain functions of the nervous system, causing increased dryness of the mucous membranes.

**B. SYSTEMIC TREATMENT WITH SPECIFIC DRUGS OR GROUPS OF DRUGS**

In this section, some drugs that are commonly used for treatment of various aspects of Sjögren’s syndrome are discussed.

**Against dryness**
- pilocarpine
- bromhexine
- acetylcysteine
- nizatidine

**Against pain**
- paracetamol (acetaminophen)
- tramadol
- opiates

**Against inflammation**
- nonsteroidal antiinflammatory drugs (NSAIDs)
- corticosteroids
- colchicine
- dapsone (diaminodiphenylsulfone)

**Immunomodulating antiinflammatory drugs**
- hydroxychloroquine
- azathioprine
- methotrexate
- cyclosporin
- mycophenolate mofetil
- cyclophosphamide

**TNF-targeted biologicals**
- infliximab
- etanercept
- adalimumab

**IL-6 targeted biologicals**
- tocilizumab or atlizumab

**Anti-B lymphocyte biologicals**
- rituximab
- epratuzimab
- belimumab

**Anti-T lymphocyte biologicals**
- abatacept
- efalizumab
- alefacect
Pilocarpine

The purpose of treatment with pilocarpine is to stimulate the salivary and lacrimal glands into making more saliva and tear fluid. Other exocrine (moisture secreting) glands sometimes also function better such as those in the nose, ears, Eustachian tube, oesophagus and other parts of the intestines, skin and vagina. The effect starts half an hour after taking the dose and lasts 3-5 hours (see figure 5.3).

Pilocarpine improves the production of saliva and tears, resulting in better protection of mucous membranes. It can be prescribed as capsules or as tablets. The starting dose is usually 4x 5 mg/day. The patient can choose when to take the dose, but taking it half an hour before meals can improve eating. The effect may improve after a few months.

Common side effects of the drug include flushing, sweating and more frequent urination than usual. The patient can decide whether to continue despite the side effects, or whether it is preferable to stop.

7.5% of people over the age of 65 years experience mild symptoms of dizziness. The pupil may become smaller. This can be a disadvantage for some people because it can make seeing in the dark more difficult, which is particularly important when driving a car.

Depending on the drug’s effect and any side effects, the dose can be adjusted. In the case of “normal” body weight, the maximum dose is 10 mg 4x per day. This dose can be tried if the effect of the standard dose of 5 mg 4x per day is insufficient and there are no bothersome side effects. Instead of 4x 10 mg, it is also possible to take 8x 5 mg or if necessary 16x 2.5 mg: the advantage of taking a lower dose more frequently is that you avoid high peaks of pilocarpine in the blood. This is especially important if bothersome sweating occurs as a side effect half an hour after taking the pilocarpine. If no improvement is seen within a few months even with the higher dose, the pilocarpine treatment can be immediately stopped. It is also possible to take pilocarpine as and when needed.

Pilocarpine can be taken in combination with other medicines. However, in the case of betablockers (mainly used to treat heart disease, and for high blood pressure in the past), it is advisable to start with a low dose because the combination may cause heart conduction disorders. If a patient benefits from taking pilocarpine, it can be used on a long-term basis. Studies show that oral symptoms improve in about 60% of patients and eye symptoms in almost half of the patients.

Pilocarpine comes from a plant, the *Pilocarpus jaborandi*. It acts through binding to the M3 muscarinic receptor on gland cells as normally occurs with acetylcholine (see chapter on cause). Recent research has shown that acetylcholine does not bind successfully to M3 receptors in patients with Sjögren’s syndrome because there are antibodies to the M3 receptor that block this. The effective action of pilocarpine in 60% of patients with Sjögren’s syndrome, irrespective of the duration of the disease (!), indicates that the diminished function of the glands is not only the consequence of damage to the glands but is above all due to the reduced possibility of acetylcholine reaching the M3 receptor. It is conceivable that the inflammation of the glands may be the consequence of the M3 antibodies binding to the M3 receptor. If this is indeed the case, treatment with pilocarpine should in the long term also have a positive effect on the inflammation. In the future we are likely to see more M3 receptor agonists appearing on the market with longer lasting and more specific binding to the M3 receptor, for example cevimeline.

Local pilocarpine and cevimeline

**Eyes**

Pilocarpine eye drops are used to treat increased eye pressure (glaucoma). These drops should not be used for the treatment of dry eyes in Sjögren’s syndrome because they do not help this condition and can worsen eye disorders. Nor should the drops be drunk in a glass of water. The amount of pilocarpine that is swallowed in this way can greatly vary.

**Mouth**

A randomized-controlled trial published in 2002 tested a pilocarpine mouthwash formulation, used orally for 1 minute in healthy individuals. Increased objective salivary flow persisted for 75 minutes for both 1% and 2% pilocarpine without significant side effects.
effects. The subjective sensation of increased salivary flow was measured by visual analogue scale (VAS) and was improved in subjects using the 2% dose. This new formulation may allow the use of pilocarpine locally, thus minimizing side effects.

The efficacy of gargling 3x a day before meals using 30 mg cevimeline dissolved in 100 ml of water for each session, was tested in healthy subjects and patients with Sjögren’s syndrome. Cevimeline gargle markedly increased salivary flow rates in 2 of 5 patients. In the remaining 3, the effect was negligible. In 3 of the 5 patients clinical symptoms improved subjectively. No adverse effects were seen. These preliminary data indicate that further studies are warranted with local oral treatment with pilocarpine and cevimeline. However, a 2% pilocarpine solution contains 20 mg of pilocarpine per ml mouthwash and the swallowing of 1 ml of the mouth wash is a overdose.

Level of evidence for the efficacy of systemic pilocarpine

Two randomized-controlled trials in the Sjögren’s syndrome literature met the highest level of evidence. In both studies, pilocarpine 5 mg given orally 3x or 4x daily demonstrated a significant increase in saliva output rate and improved subjective measures. Pilocarpine given orally was safe and effective in improving symptoms of oral dryness in patients with mild to severe hyposalivation. The duration of the increased salivary flow was 2-3 hours.

Pilocarpine has been approved in several countries, but not all, for the treatment of radiation-induced or Sjögren’s syndrome-induced xerostomia. Based on strong evidence, the use of pilocarpine for these conditions is recommended. The recommended dose is 5 mg orally 3x a day with titration up to 10 mg. Classification of Recommendation class I, Level of Evidence A (see box).

Bromhexine and ambroxol

Bromhexine (Bisolvon®) is a mucolytic agent used in the treatment of respiratory disorders (e.g. cough with phlegm) associated with viscid or excessive mucus. Bromhexine reduces mucus viscosity by splitting disulfide bonds linking proteins in the mucus.

Clinical studies have shown that it increases the quantity of bronchial secretion and reduces its viscosity due to depolymerization of the mucopolysaccharide fibres in mucus. The maximum effect is reached after some days. Reported side-effects have been harmless and infrequent. Ambroxol is a pharmacologically active metabolite of bromhexine and used for the same indications.

In a double-blind randomized placebo-controlled trial bromhexine 16 mg 3x a day has been found to significantly improve the Schirmer test and tear break-up time in patients with Sjögren’s syndrome. N-acetylcysteine

N-acetylcysteine is a drug used mainly as a mucolytic agent and in the management of paracetamol (acetaminophen) overdose.

N-acetylcysteine acts through its free sulfhydryl group which opens up the disulfide bonds in the mucoproteins thus lowering mucous viscosity.

Twenty-six patients with primary or secondary Sjögren’s syndrome were treated in a double-blind, cross-over trial for a four week period with oral n-acetylcysteine and placebo. Sjögren’s syndrome patients reported statistically significant improvements in ocular soreness, ocular irritability, halitosis and daytime thirst. N-acetylcysteine, but not placebo improved the van Bijsterveld score, but no effect was seen on the Schirmer test, the tear break up time or any of the laboratory tests.

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**Oxford levels of evidence and grades of recommendation**

<table>
<thead>
<tr>
<th>level</th>
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<th>grade</th>
<th>nature of recommendation based on</th>
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<td>A</td>
<td>clinical studies of good quality and consistency including at least one randomised trial</td>
</tr>
<tr>
<td>1b</td>
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<td>B</td>
<td>well-conducted clinical studies without randomised trials</td>
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<tr>
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<td>absence of directly applicable clinical studies of good quality</td>
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<tr>
<td>2b</td>
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<td>3</td>
<td>non-experimental study (comparative study, correlation study, case reports)</td>
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<tr>
<td>4</td>
<td>expert committee, expert opinion</td>
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</tbody>
</table>

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47
Nizatidine
The H$_2$ receptor antagonist nizatidine (Axid®) inhibits acetylcholinesterase, resulting in an increased availability of acetylcholine, and was recently shown to stimulate salivary secretion in healthy volunteers. In a small randomized trial, 27 patients with Sjögren’s syndrome were assigned to receive nizatidine (n=14, 300 mg/day) or another H2 blocker, famotidine (n=13, 40 mg/day; control) and followed for eight weeks.

Assessments of oral dryness were done using a visual analog scale (VAS; 1-100 mm) and the Saxon’s test, respectively. Patients receiving oral nizatidine, but not famotidine, obtained significant objective relief from their xerostomia and mild subjective improvement.

Paracetamol (acetaminophen)
Paracetamol (acetaminophen) is a widely-used analgesic and antipyretic drug. Paracetamol lacks many of the side-effects of NSAIDs. It has no antiinflammatory effects. Paracetamol-related liver disease is an important public health problem that is usually related to taking more than 4 g of paracetamol per day.

Acute overdoses of paracetamol can cause potentially fatal liver damage and, in rare individuals, a normal dose can do the same.

There are no specific data on the use of paracetamol in Sjögren’s syndrome.

Tramadol
Tramadol is a centrally acting analgesic for treatment of moderate to severe pain including neuralgias. It acts on an opioid receptor as well as the noradrenergic and serotonergic systems. It is often combined with paracetamol.

Side effects may be nausea, vomiting, sweating, drowsiness and constipation. In patients with epilepsy and in others by overdosing, it may cause seizures.

There is no literature on its use in Sjögren’s syndrome.

Opiates
Opiates are a group of drugs, such as morphine, heroin and codeine, that contain or are derived from opium. Opiates are prescribed for relief of (severe) pain but the mode of action is poorly understood.

Certain patients may require 10 times the dose to get the same level of pain relief as others. Side effects such as nausea or sedation can be debilitating to some and nonexistent for others.

Common adverse effects include euphoria, itching, nausea, vomiting, drowsiness, dry mouth, miosis, orthostatic hypotension, urinary retention and constipation.

The addiction potential also varies among people. Groups at particular risk are chronic pain patients, health care providers and drug abusers.

There is no literature on the use of opiates in Sjögren’s syndrome but side effects such as dry mouth and constipation may limit their use.

Non-steroidal anti-inflammatory drugs (NSAIDs)
There are various groups of anti-inflammatory drugs such as corticosteroids (e.g. prednisolone), prostaglandin synthesis inhibitors and others (e.g. HCQ and colchicine).

Non-steroidal anti-inflammatory drugs (NSAIDs) reduce the inflammation by inhibiting cyclooxygenase-1 and 2 (cox-1 and cox-2 respectively) and corticosteroids on phospholipase A$_2$. **Table 5.1 Examples of effects on cox-1 and cox-2 of prostaglandin synthesis inhibitors**

<table>
<thead>
<tr>
<th>inhibition of</th>
<th>cox-1 + cox-2</th>
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<th>selective cox-2</th>
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<td>celecoxib</td>
<td>rofecoxib $^a$</td>
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<td>meloxicam</td>
<td>etoricoxib</td>
<td>valdecoxib $^a$</td>
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<tr>
<td>tenoxicam</td>
<td>tiaprophenic acid</td>
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<td></td>
</tr>
</tbody>
</table>

$^a$ rofecoxib and valdecoxib were withdrawn from the market in 2004-05 due to an increased risk of cardiovascular events (including heart attack and stroke)
ase-2 (cox-2) and are therefore called prostaglandin synthesis inhibitors. Until recently, all NSAIDs on the market also inhibited cyclo oxygenase-1 (cox-1). Table 5.1 shows NSAIDs classified according to inhibition of cox-1 and/or cox-2.

Cox-2

When tissue damage occurs, arachidonic acid is formed from phospholipids of the membrane of white blood cells with help of phospholipase A2. With the help of cox-2, this in turn forms prosta glandins (PGs). These PGs cause inflammation and symptoms such as pain, fever and vasodilation (figure 5.4).

Cox-1

Prior tissue damage is not necessary for the production of cox-1. Cox-1 is continually being formed and not especially by white blood cells. Cox-1 is needed, for example, for the production of PGs that protect the gastric mucosa (lining of the stomach) and for the production of thromboxane A2 (TxA2) that stimulates the aggregation of platelets and causes constriction of blood vessels.

NSAIDs that also inhibit cox-1 consequently may cause damage to the gastric mucosa while hemostasis (blood stanching) is affected in all users. This unfortunate combination of effects may cause gastric mucosa bleeding. This risk is reduced if a proton pump inhibitor (e.g. omeprazole) that inhibits the formation of gastric acid or miso prostol (restores the prosta glandin effect on the gastric mucosa) is also taken.

Selective cox-2 inhibitors (coxibs)

Due to the absence of the cox-1 effect, the risk of gastric adverse effects is smaller and the function of the platelets is not affected. This results in a lower risk of gastrointestinal complaints, perforations, ulcers and bleeding. The risk of gastrointestinal events caused by coxibs is somewhat less than half the risk of old NSAIDS.

Inhibition of cox-2 has been found to increase the risk of cardiovascular thrombotic events such as heart attack and stroke. This is due to the inhibition of the prostacyclin PGI2 (figure 5.4). PGI2 is a natural inhibitor of aggregation of platelets and induces dilatation of blood vessels. In healthy subjects, the prothrombotic effect of TxA2 is counteracted by the antithrombotic effect of PGI2.

Coxibs and low-dose aspirin

In the treatment of cardiovascular disease, inhibition of the function of platelets (a cox-1 effect) is often desirable. If necessary, the selective cox-2 inhibitors can be combined with low dose aspirin, unlike ibuprofen and indomethacin that render low dose aspirin ineffective. However, cardiovascular disease is a contraindication for the use of all NSAIDs with the possible exception of naproxen.

The balance between effects of TxA2 and PGI2

Old NSAIDs reduce both TxA2 and PGI2, and the equilibrium between the opposite effects is therefore more or less sustained. This is probably true for patients with no systemic inflammatory disease such as osteoarthritis, but may be not true for patients with rheumatoid arthritis, for example.

Low-dose aspirin (40-100 mg/day) only blocks the formation of TxA2 and is therefore antithrombotic. Coxibs inhibit PGI2 in a dose-dependent way and have a pro thrombotic effect in susceptible persons. However, recent data suggest that the old NSAIDs (with the possible exception of naproxen) have similar cardiovascular adverse effects.

Other adverse effects

The coxibs unfortunately have the same adverse effects as the old NSAIDs in the form of a possible rise in blood pressure, impairment of the kidney function in the case of a pre-existing kidney disorder, fluid retention, congestive heart failure and constipation.
Other favourable effects

Usually, a high level of COX-2 expression is found in cancer cells. Protective effects of NSAIDs including aspirin and coxibs, have been found on the prevention and treatment of cancers.\(^{172}\) Examples include: nonmelanoma skin cancers, breast cancer, and colorectal cancer.\(^{171}\)

Several double-blind, randomized, placebo controlled studies suggest that celecoxib is an effective adjuvant agent in the management of patients with major depression.\(^{167,168}\)

Conclusion

If the use of painkillers/anti-inflammatory drugs is necessary, a choice has to be made between one from the old NSAIDs or one from the new coxibs. For patients with previous gastric ulcers, perforation or bleeding, a coxib is the first choice. This also applies to patients on anticoagulant therapy. For patients with ischemic vascular disease (thrombosis, heart attack, stroke) or with risk factors, it may be safer to combine naproxen and a proton pump inhibitor such as omeprazol. This may also apply to healthy women on oral contraceptives.

However, the results of ongoing (e.g. EDGE, EDGE II, MEDAL)\(^{77}\) and new studies are necessary before final conclusions can be drawn with regard to the cardiovascular safety of preparations.

Corticosteroids

Corticosteroids are synthetic forms of cortisol, a hormone made by the adrenal glands. Well-known examples are prednisone, prednisolone, dexamethasone and hydrocortison.

High doses of corticosteroids (e.g. prednisolon) should only be considered in life-threatening or otherwise severe irreversible complications. The risks of side-effects such as osteoporosis, high blood pressure (hypertension), diabetes mellitus, muscle weakness, cataract, glaucoma, puffy face, thin skin and infections, have to be accepted under these circumstances, but can sometimes be reduced by certain measures. Increased bone resorption due to prednisolone can be counteracted by e.g. alendronate 1x a week one tablet of 70 mg or etidronate/calcium carbonate.

Colchicine

Colchicine inhibits neutrophil and monocyte chemotaxis, collagen synthesis and mast cell histamine release. It is mainly used for gout for about 2600 years now. More recent applications are Behçet’s disease, familial mediterranean fever, psoriasis, vasculitis, systemic sclerosis including CREST syndrome, sarcoidosis, idiopathic pulmonary fibrosis\(^{144}\) and recurrent aphthous stomatitis.

Gastrointestinal side affects are common but are usually harmless and dose dependent. Other side effects are astonishing absent.\(^{141}\) Although uncommon, colchicine poisoning may cause severe systemic effects. For acute gout high doses have been used: the FDA noted 117 nonoverdose deaths (some recent) that were associated with oral colchicine (with 51% involving an interaction between colchicine and clarithromycin).\(^{165}\) Clinical trials of colchicine showed that lower doses were as effective as higher doses (4.8 mg over 6 hours) and produced fewer side effects. Toxic doses produce, in addition to nausea and vomiting, bone marrow suppression often leading to sepsis, hypocalcemia, adult respiratory distress syndrome, and direct cardiotoxic effects.\(^{143,149}\)

In Sjögren’s syndrome colchicine may be used for hypergammaglobulinemic purpura, other forms of vasculitis and arthritis. A common and safe dosage is 0.5 mg, 1-3x a day. Liver enzymes should be tested after three months.

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a steroid hormone precursor produced from cholesterol by the adrenal glands and several other organs. It is the precursor of androstenedione, which can undergo conversion to testosterone and the oestrogens oestrone and oestradiol.

Low levels of serum DHEA have been found in SLE, RA and Sjögren’s syndrome. It was subsequently
hypothesized that normalizing DHEA levels could be beneficial. There is some evidence that this may be true in SLE but randomized double-blind placebo-controlled trials showed no evidence of efficacy in Sjögren’s syndrome.\textsuperscript{146,147} Moreover, Pillemer et al \textsuperscript{146} warn against the use of unregulated DHEA supplements, since long-term adverse consequences of exposure to this hormone is unknown.

**Dapsone (diaminodiphenylsulfone)**

Dapsone (diaminodiphenylsulfone, DDS) is available as a drug since the 1940s and continues to be a powerful drug in many skin diseases including leprosy.\textsuperscript{151}

As an anti-infective agent, it is also used for treating malaria and for Pneumocystic jiroveci (carinii) pneumonia in AIDS patients. Dapsone has been found to be uniquely effective against a number of non-infectious inflammatory diseases, of which dermatitis herpetiformis (a skin disease related to celiac disease) is the best known. The response of this disease to the drug is so dramatic (the pruritus is relieved within 48-72h) that it has even been considered as being a diagnostic indicator.

Dapsone acts against bacteria and protozoa in the same way as sulphonamides. Dapsone also inhibits the release and function of neutrophil lysosomal enzymes but the antiinflammatory action is not fully understood.

**Dapsone in Sjögren’s syndrome**

No clinical studies are available on the use of dapsone in Sjögren’s syndrome. Case reports and the use of dapsone for clinical features that may also occur in Sjögren’s syndrome, warrant the use of dapsone in selected cases of Sjögren’s syndrome when first choice therapies failed or were contraindicated.

Examples are idiopathic thrombocytopenic purpura, urticarial vasculitis and leukocytoclastic vasculitis.\textsuperscript{151-153}

**Contraindications and monitoring of patients**

Dapsone is used by millions of patients without serious problems. Rare but potentially harmful adverse effects necessitate careful monitoring of patients under this treatment. Dapsone is considered unsafe in the following conditions: severe anemia, porphyria, deficiency of glucose-6-phosphate dehydrogenase, glutathione reductase or methemoglobin reductase, allergy to sulfonamides, or significant liver disease. It should not be paired with other hemolytics or dideoxynosine. Before starting therapy, a complete blood count, reticulocyte count, glucose-6-phosphate dehydrogenase level, liver function studies, urinanalysis and renal function tests should be performed. During therapy, complete blood count, reticulocyte count, platelet count and leukocyte count with differential should be obtained weekly for the first month, then twice per month during the next two months and every three months thereafter. Liver and renal function should be tested every three months.

Methemoglobin levels should be obtained in patients who become symptomatic (see below) for methemoglobinemia.\textsuperscript{151}

**Adverse effects**

Long-term administration of dapsone at standard doses (100 mg/d) usually results in methemoglobinemia of 15%. Methemoglobin is a form of hemoglobin in which the iron in the heme group is Fe\textsuperscript{3+} and not Fe\textsuperscript{2+} as in normal hemoglobin. Methemoglobin, however, cannot carry oxygen. Normally 1-2% of people’s hemoglobin is methemoglobin. Methemoglobin levels <20% are not usually associated with symptoms. Dyspnea, nausea and tachycardia usually occur at levels of 30% or above, while lethargy, stupor and deteriorating consciousness occur as methemoglobin levels approach 55%. Levels of 70% are usually fatal. Agranulocytosis is, unlike methemoglobinemia, a severe idiosyncratic reaction. Idiosyncratic drug reactions are rare, unpredictable and dose-independent drug reactions. The probable mechanism is a complex immune-mediated cytotoxicity. For unknown reasons, the risk of agranulocytosis in patients with dermatitiss herpetiformis is more than 25-fold (1 of 240-425) compared with other patients, whereas this side effect in patients with leprosy is almost unknown.\textsuperscript{151}

Another serious idiosyncratic adverse effect is the **dapsone-induced hypersensitivity syndrome**. The unpredictability and potential severity of this reaction make it a major concern in clinical practice. Although this reaction to dapsone is rare considering the widespread use of the drug, it ranks high among drugs that cause this syndrome. Dapsone-induced hypersensitivity syndrome usually appears four or more weeks after initiation of therapy. Symptoms include a mononucleosis-like rash with fever and lymphadenopathy. Involvement of other organs varies and includes the liver (hepatomegaly, icterus, hepatitis and hepatic encephalopathy), lymphadenopathy, eosinophilia, and others. The course of the disease is also variable, but it may last four weeks or more and fatalities have been reported.

Exanthematous skin eruptions usually resolve within two weeks of stopping dapsone, although patients in whom Stevens-Johnson syndrome or toxic epidermal necrolysis develops have increased morbidity and mortality.
Hydroxychloroquine

Hydroxychloroquine (Plaquenil®) and chloroquine (Nivaquin®) are among the safest drugs with anti-inflammatory and disease-modifying properties. These effects are not exerted through inhibition of cox-1 or cox-2 (see further). It often takes 2-6 months before an improvement can be seen.

Although we are talking here about hydroxychloroquine (HCQ), chloroquine has similar but not identical effects and side effects: 3.0 mg chloroquine is equivalent to 6.5 mg HCQ. Hydroxychloroquine has less side-effect than chloroquine (see next pages).

Effects

Disease-modifying means that the drug has a positive effect on the course of the disease and that it does not simply suppress symptoms. In addition to its original use for the treatment and prevention of malaria, it has been successfully used for around 50 years for the long term treatment of various chronic conditions such as rheumatoid arthritis and forms of lupus erythematosus (LE) such as discoind LE, subacute cutaneous LE and systemic LE.

More recently, it has been used to treat diseases such as Sjögren’s syndrome, sarcoidosis, polymyositis (inflammatory muscle disease), vasculitis, porphyria cutanea tarda, cutaneous manifestations of dermatomyositis, asthma, hyperlipidemias and thromboembolic prophylaxis for patients with antiphospholipid antibodies.

All drugs have in addition to the desired effects adverse side-effects. Hydroxychloroquine, however, also has several unexpected favourable side-effects (see table 5.2).

Hydroxychloroquine (Plaquenil®)

- the elimination half-life is about 40 days; this results from extensive tissue uptake and slow redistribution back into the blood from large tissue repositories
- it is widely distributed throughout the body, accumulating in blood cells, kidney, liver, lung and eye
- it is partially converted to de-ethylated metabolites in the liver and is eliminated principally via the kidneys
- it also forms an ether glucuronide that is excreted in the bile; about 25% is excreted renally unchanged

Table 5.2 Favourable effects of hydroxychloroquine (HCQ) other than anti-inflammatory and disease-modifying

- HCQ has a lipid lowering effect even if the patient takes corticosteroids
- it directly reduces the binding of antiphospholipid antibody β2-glycoprotein I complexes to phospholipid bilayers; this may be one of the explanations of the antithrombotic effects of HCQ in patients with the antiphospholipid syndrome
- it prevents vitamin D deficiency in SLE patients
- among SLE patients, steroid treatment is associated with the highest degree of vascular damage, and HCQ is associated with the lowest degree of vascular damage
- HCQ treatment is associated with later onset of SLE in people with autoantibodies
- HCQ has a protective effect on survival of SLE patients which is evident even after taking into consideration the factors associated with treatment decisions
- SLE patients on antimalarials (mainly HCQ) have a 6-7x decreased risk for various cancers
- HCQ improves glucose metabolism and insulin sensitivity among patients with SLE
- it reduces the risk of infection in hospitalized patients with rheumatoid arthritis (RA)
- RA patients using HCQ have a reduced (62% of normal risk; 23% after 4 years) risk of diabetes
- the prevalence of aged-related macular degeneration (AMD) in RA cases is about 10-fold lower than in general populations of similar racial origin; this is attributed to the use of antinflammatory drugs including HCQ
- it is efficous to treat severe granulomatous complications in a patient with CGD (chronic granulomatous disease)
- HCQ has antihyperglycaemic properties in patients with type 2 diabetes mellitus
- and do not forget: it is an antimalarial too
HCQ in Sjögren’s syndrome

There is only one double-blind placebo-controlled study on HCQ treatment in Sjögren’s syndrome. This two-year cross-over trial in 19 patients from two centers was done by Kruize et al. The only effect that was found was an improvement of hyperglobulinaemia, ESR (erythrocyte sedimentation rate) and IgM.

In a retrospective study of 50 Sjögren’s patients, Fox et al. found the following effects of HCQ:

- sustained improvement of local symptoms (painful eyes, painful mouth)
- improvement of systemic manifestations (arthralgias and myalgias) after treatment
- a significant improvement in ESR and IgG levels

In an open-label study of HCQ, Tishler et al. saw a significant reduction of some salivary inflammatory markers at the end of 12 months as well as partial clinical effects.

Inflammatory conditions in Sjögren’s syndrome that can be treated with HCQ are those of the salivary glands, muscles, joints, blood vessels and nerves. Laboratory abnormalities such as increased ESR, anaemia and increased serum IgG can show improvement. HCQ also reduces the risk of thrombosis caused by antiphospholipid antibodies, can lower cholesterol levels and probably reduces the risk of a non-Hodgkin lymphoma and other malignancies.

Symptoms for which a trial treatment would be worthwhile include severe joint and muscle pain, recurrent flu-like feeling or fever and fatigue.

In addition to its use for inflammatory conditions, HCQ can also sometimes be used for symptoms without objectively determinable abnormalities.

Side effects

Side effects are relatively mild and uncommon. They mainly concern allergic reactions (red rash, fever), increased sensitivity to sunburn, pigment changes in the skin or hair loss that recovers after stopping treatment (see table 5.3).

Exacerbation or manifestation of (subclinical) disease

Psoriasis

Psoriasis is often exacerbated but not an absolute contra-indication.

Myasthenia gravis

A rare side effect of HCQ is double vision and/or increase in muscle weakness. This may be an indication of a hitherto undiagnosed mild form of myasthenia gravis and should be reported to the specialist (see also chapters 2, 7 and 13).

Heart

Conduction disorders

A high incidence of heart conduction disorders, including bundle-branch block and incomplete or complete atrioventricular block, has been observed among patients treated with chloroquine. HCQ, however, has not found to be associated with heart conduction disorders.

Cardiomyopathy

An extremely rare but possibly fatal side effect of HCQ is cardiomyopathy. Thirteen cases have been described to date. Several diseases that are treated with HCQ can cause cardiomyopathy themselves. Examples are myocarditis, vasculitis, SLE, systemic sclerosis. HCQ-associated cardiomyopathy is characterized by myocyte vacuolization at light microscopy and both myelin figures and curvilinear bodies on electron microscopy. Recently, a 64-year-old women with SLE was described, treated for more than 10 years with prednisone and HCQ, who presented with severe progressive dyspnea on exertion. Endomyocardial biopsy revealed sarcoplasmic clearing and vacuolization on light microscopy and myelinoid

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**Table 5.3 Possible adverse effects of hydroxychloroquine treatment (see text for further information and references)**

- Hypersensitivity reactions (rash, fever)
- Increased sensitivity to sunburn
- Pigment changes
- Reversible diffuse hair loss
- Exacerbation of (subclinical) psoriasis
- Temporary blurred vision
- Exacerbation of subclinical myasthenia gravis
- Maculopathy (preventable)
- Myopathy (rare)
- Cardiomyopathy (very rare; partially reversible)
- Alterations in hearing (very rare)

**Hydroxychloroquine and heart conduction**

Hydroxychloroquine, in contrast to chloroquine, has not found to be associated with heart conduction disorders.

Costedoat-Chalumeau et al (2007)
and curvilinear bodies on electron microscopy. HCQ toxicity was diagnosed and the medication was discontinued. The patient was asymptomatic within 9 months. Follow-up revealed a normal left ventricular systolic function and grade 2/4 diastolic dysfunction. Wall thickness had normalized.

Pregnancy and lactation
More than 250 pregnancies of SLE patients on HCQ resulting in live births have been reported and no increase in the rate of birth defects, retinal toxicity and ototoxicity has been demonstrated.

Data concerning lactation and HCQ treatment are rare. However, the amount of HCQ received by children through lactation seems very low. In conclusion, HCQ should probably be maintained throughout pregnancy in patients with SLE and it does not seem necessary to advise against breastfeeding.

Hearing disorders
Alterations in hearing have been ascribed to HCQ in three patients. It is known that chloroquines accumulate and fix selectively in melanocytes, with its ototoxicity resulting in variable injuries to the cochlear sensory hair cells, decrease in neuronal population, loss of supporting hair cells, and atrophy of stria vascularis. It is supposed that ototoxicity is associated with a similar deposit mechanism of chloroquines in the internal ear caused by a prolonged exposure time and by high cumulative doses.

Eyes

Blurred eyesight
During the first days of treatment, the patient may experience blurred eyesight. This is perfectly innocent, has nothing to do with retina defects through overdose and can be counteracted by halving the dosage in the first week (usually 200 mg/day).

Maculopathy
The most important side effect with long-term use is maculopathy. New data have shown that the risk of toxicity increases sharply toward 1% after 5 to 7 years of use, or a cumulative dose of 1000 g, of hydroxychloroquine. The risk increases further with continued use of the drug. Maculopathy caused by HCQ is a double-sided disorder of the retina with defects in the field of vision. With early diagnosis and stopping the medication, the condition either recovers or progresses no further. It should be noted that the risk for maculopathy is much smaller for HCQ than for chloroquine.

High or low risk of maculopathy
It is essential to base the dosage on body weight and kidney function. It is recommended to go no higher than 6.5 mg/kg/day HCQ or 3.0 mg/kg/day chloroquine. Note that the body weight refers to the lean body mass (LBM). This is because chloroquines are not well absorbed in fatty tissue, so body fat should not be counted. See table 5.4.

Although HCQ can be given even if a patient already has eye defects (apart from a chloroquine maculopathy) it is usually suggested to have an eye check in the first year of treatment. This does not need to be done before the treatment since retina defects caused by HCQ have never been described in association with treatment of less than 9 months. The timing of the

Overdosing of HCQ is going on today...........

The importance of dosing on the basis of the lean body mass is illustrated by a study of Payne et al. They reviewed the medical records of consecutive patients with hydroxychloroquine retinopathy in of the Emory Eye Center (Emory University, Atlanta, Georgia, USA) between 1 January 2004 and 31 December 2008. A total of seven patients were included for analysis. While every patient received 400 mg of hydroxychloroquine per day, every patient exceeded the recommended daily dosage allowance (6.5 mg/kg/day). The mean daily dose of hydroxychloroquine was 8.2 mg/kg/day (range: 6.8-13.6 mg/kg/day).
next retina check-up depends on how high the risk of maculopathy is estimated to be. This risk is determined by the LBM, the kidney function and the length of time for which HCQ has been used.

A patient is in the **low risk group** if the dose is less than 6.5 mg/kg LBM/day HCQ and the patient has been taking the drug for less than 5 years. It is important for the upper limit of 6.5 to be lowered in proportion to any diminished kidney function.

A patient belongs to the **high risk group** if the dose is > 6.5 (or lower in the case of diminished kidney function) mg/kg LBM/day HCQ or if the patient has been taking the drug for more than 5 years. For low risk patients, a check-up is only necessary after 5 years. For high risk patients, an annual check-up is recommended. My personal impression is that the latter recommendation is correct if the dose taken has been too high (on the basis of LBM and kidney function), but is unnecessarily stringent if the patient is only in the high risk group due to taking the drug for more than 5 years.

For many patients with a weight of 60-65 kg, a dose of 400 mg HCQ per day for the first three months, after 3-6 months, the daily dose can usually be as low as two-thirds of the maximum daily dose, or even lower, depending on the effect of hydroxychloroquine.

<table>
<thead>
<tr>
<th>length (cm)</th>
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Table 5.4 Maximum daily dose\(^1\) of hydroxychloroquine (HCQ) in relation to the length and lean body mass\(^2\).

**It is extremely important to decrease the dose proportionally in case of diminished kidney function (see text) and to use the real body weight in case this is less than the lean body mass (LBM).**

Example: woman with length of 168 cm and weight of 51 kg. Weight (51 kg) is less than LBM (60 kg), so use the data on the line with a LBM of 51 kg (corresponding length of 158 cm): the maximum numbers of tablets is 11 per week and not 13 per week.

\(^{1}\) after 3-6 months, the daily dose can usually be as low as two-thirds of the maximum daily dose, or even lower, depending on the effect of hydroxychloroquine.

\(^{2}\) the lean body weight for men, in kilograms, is equal to 50 plus 2.3 kg for every inch over 5 feet in height; the lean body weight for women, in kilograms, is equal to 45.5 plus 2.3 kg for every inch over 5 feet in height.
followed by 200 mg/day appears to work well. If the symptoms return after reducing the dose, dosages of 200 and 400 mg can be taken on alternate days or the patient can return to 400 mg/day.


Interactions of HCQ with other drugs
HCQ can be combined with almost all drugs. Relevant interactions may occur with digoxine and proton-pump inhibitors.

Digoxin
HCQ may increase the plasma concentration of digoxine, a drug used for heart failure.

Proton-pump inhibitors
The proton pump inhibitors (PPI) omeprazole (Losec®), lansoprazole, pantoprazole, esomeprazole (Nexium®) and rabeprazole suppress gastric acid secretion by inhibiting the gastric H+K+ ATPase at the secretory surface of the gastric parietal cells.

Chloroquine and HCQ accumulate in the acidic environment of macrophage lysosomes and raise intralysosomal pH levels, with the resultant decreased ability of macrophages to process antigens.

PPI may compete with HCQ and/or the higher lysosomal pH would inhibit the accumulation of HCQ at its site of action, thus mitigating its immunomodulatory and antimalarial effects.

The potential antagonising effect of PPI inhibitors on the efficacy of HCQ should be born in mind when facing unresponsive to antimalarials.157

Azathioprine
Azathioprine (Imuran®), introduced in 1963, is a purine analogue that interferes with the synthesis of DNA and RNA. Effects are a decrease of the circulating lymphocyte count and inhibition of antibody production.

Common (side) effects are leukopenia (dose dependent) and gastrointestinal symptoms such as nausea, vomiting and diarrhea. In dosages up to 150 mg a day, it is considered a rather safe drug. For many indications, it is continued during pregnancy. Potential fatal drug interactions may occur with allopurinol, a drug used for gout and hyperuricemia.

It has been widely used in the past as an immuno-suppressant for organ transplantation. Today it is mainly used for autoimmune diseases such as SLE, Behçet’s disease and Crohn’s disease.

Price et al 145 performed a 6-months double blind placebo controlled trial of low dose (1 mg/kg/day) azathioprine in the treatment of 25 patients with primary Sjögren’s syndrome. They found no significant change in disease activity variables when measured clinically, serologically, or histologically and conclude that low dose azathioprine does not have a role as a disease modifying agent in Sjögren’s syndrome.

Case reports have been published on positive effects of azathioprine (2 mg/kg/day) combined with corticosteroids for severe central nervous system involvement, interstitial lung diseases, interstitial nephritis or autoimmune hepatitis.

Methotrexate
Methotrexate (MTX) is a structural analogue of folic acid. Via inhibition of a folic acid reducing enzyme, MTX results in the cessation of the synthesis of various purine metabolites and also inhibits protein synthesis. High doses are used for cancer therapy while low doses are mainly used for treating rheumatoid arthritis. Low doses have little effect on T lymphocytes but mainly reduce immunglobulin levels.

Skopouli et al 159 performed an open, one-year pilot study of MTX (0.2 mg/kg body weight taken weekly). Seventeen patients with primary Sjögren’s syndrome were enrolled. Outcome was determined on the basis of clinical and laboratory parameters. Weekly administration of MTX resulted in improvement of the main subjective symptoms (dry mouth and eyes) as well as in the frequency of parotid gland enlargement, dry cough and purpura. However, no improvement in the objective parameters of dry eyes and dry mouth were observed. Persistent asymptomatic elevation of the hepatic transaminase levels led to a dosage reduction in 7 patients (41%). The authors concluded that weekly MTX may be an acceptable form of therapy for Sjögren’s patients and that double-blind trials were needed to substantiate the efficacy of this therapeutic modality. This was said in 1995 and 15 years later, such trials have not been performed to date.

Cyclosporin
Cyclosporin (Neoral®), a drug derived from a fungus, is
used for organ transplantation and many autoimmune diseases. Cyclosporin (CyA) inhibits intracellular calcineurin and as a consequence the transcription of genes for cytokines such as IL-2 in the nucleus of activated T lymphocytes.

The major adverse effect is renal toxicity which is usually dose related and reversible. Other adverse effects are hypertension, hirsutism and gingival hyperplasia. CyA has clinically important interactions with many drugs such as antifungals, calcium channel antagonists, ACE inhibitors and statins.

Grapefruit juice may dramatically increase cyclosporin concentrations. However, in the great majority of patients, CyA, in dosages not exceeding 4 mg/kg per day and the monitoring of renal function and blood pressure, is a safe and effective drug for many autoimmune diseases such as psoriasis, Behçet’s disease, subacute cutaneous lupus erythematosus and inflammatory eye diseases such as various forms of uveitis.

Drosos et al. studied the efficacy and toxicity of cyclosporin A (CyA) in 20 patients with primary Sjögren’s syndrome. The dose of CyA or placebo was 5 mg/kg of body weight daily. Among the 20 patients, 10 received CyA and 10 placebo. Patients treated with CyA improved in subjective xerostomia in comparison with patients treated with placebo. Subjective xerophthalmia and recurrent parotid gland enlargement did not differ in the two groups. No change in Schirmer’s test and stimulated parotid flow rate was observed in either group. In contrast, the histopathological lesion of patients treated with CyA remained unchanged in most of the patients, while in the placebo treated group the lesion deteriorated. Laboratory parameters did not change before or after treatment in either group. The only clinical side effect observed in the CyA treated group was hypertrichosis. This study was published in 1986 and no other studies on the efficacy of CyA could be found in the literature to date.

Mycophenolate sodium and mofetil
Mycophenolate is derived from the fungus Penicillium stoloniferum. It inhibits inosine monophosphate dehydrogenase, which is the enzyme that controls the rate of synthesis of guanine monophosphate in the de novo pathway of purine synthesis essential in the proliferation of B and T lymphocytes.

Mycophenolates are increasingly used for the prevention of organ transplant rejection, as well as for many immune-mediated diseases.

In a open-label pilot trial, the efficacy of mycophenolate sodium (Myfortic®, MPS) was studied in patients with primary Sjögren syndrome refractory to other immunosuppressive agents. Eleven patients were treated with MPS up to 1440 mg daily for 6 months. MPS treatment resulted in subjective improvement of ocular dryness and a reduced demand for artificial tears. However, no significant alterations of objective parameters for dryness of eyes and mouth were observed, although a substantial improvement of glandular functions occurred in two patients with short disease duration. In addition, treatment with MPS resulted in significant reduction of hypergammaglobulinemia and rheumatoid factors as well as an increase of complement levels and white blood cells.

In a small open study in patients with interstitial lung disease as part of various systemic autoimmune diseases, MPS was found to be safe and well tolerated. It allowed a reduction or discontinuation of prednisone (the mean daily dose decreased from 58 to 1.4 mg) without worsening of symptoms or progression of disease. The investigators concluded that MPS was less toxic and a potentially more effective agent than cyclophosphamide. Further investigations about the efficacy and safety of MPS in pSS have to be performed in larger numbers of patients.

Cyclophosphamide
Cyclophosphamide (Endoxan®, Cytoxan®) is a nitrogen mustard alkylating agent. It is used to treat various types of cancer, some autoimmune disorders (e.g. systemic lupus erythematosus and severe systemic vasculitis (e.g. Wegener’s granulomatosis, polyarteritis nodosa)). It is an important drug with unique beneficial effects on these diseases, but it also has major side effects, even for the relatively low doses (1-2 mg/kg body weight) that are used for autoimmune diseases and systemic vasculitis. Examples are hair loss, bone marrow suppression, sterility, hemorrhagic cystitis, induction of lymphoma or skin cancer, and secondary infections. For these reasons, cyclophosphamide (CP) is only used for those life-threatening conditions for which it’s efficacy has been firmly established.

No studies have been performed on CP for the treatment of Sjögren’s syndrome in general as it is too dangerous for general application. Case reports have been published on the efficacy of CP for very severe complications of Sjögren’s syndrome such as interstitial lung disease, aggressive MALT lymphoma, myelopathy, cranial nerve neuropathy, and severe forms of glomerulonephritis. For some indications, CP is given intravenously once a month.

CP should only be used in Sjögren’s syndrome with life-threatening complications for which no other
treatment options are available.

**Cytokine and cytokine-receptor-targeted therapy**

**TNF-targeted therapy**

Infliximab (Remicade®), etanercept (Enbrel®) and adalimumab (Humira®) inhibit the effect of TNF-α, a cytokine that plays a crucial role in causing inflammation by means of predominantly T-cell-mediated tissue damage. TNF-targeted therapies are being used for many rheumatic and autoimmune diseases such as rheumatoid arthritis (RA), ankylosing spondylitis, Crohn’s disease, and psoriasis. The prognosis and quality of life of patients with these diseases have improved dramatically. However, safety concerns persist due to the seriousness and unexpected nature of some rare adverse events that have been seen with all 3 agents.

**Infliximab**

Infliximab (Remicade®) is a mouse-human chimeric antibody to TNF-α. In Sjögren’s syndrome, it has been found inefficacious in a multicenter, randomized, double-blind, placebo-controlled trial with 103 patients. The patients were randomly assigned to receive infliximab infusions (5 mg/kg) or placebo at weeks 0, 2, and 6 and were followed up for 22 weeks. All patients fulfilled the American-European Consensus Group criteria for primary Sjögren’s syndrome and had active disease.

**Etanercept**

Etanercept (Enbrel®) is a human fusion protein consisting of the extracellular ligand-binding portion of the human TNF receptor linked to the Fc portion of human IgG1. In a 12-week randomized, double-blind, placebo-controlled trial with 14 patients with Sjögren’s syndrome in each group, etanercept 25 mg twice weekly was clinically inefficacious.

**Adalimumab**

Adalimumab (Humira®) is a fully human monoclonal antibody. There are no data on the efficacy of adalimumab in Sjögren’s syndrome to date. As etanercept and infliximab have not been found to be efficacious, the same can be expected for adalimumab.

**Lack of efficacy of TNF-targeted therapy in Sjögren’s syndrome**

A recent study in Sjögren’s syndrome indicated that before treatment, salivary gland focus scores did not correlate with circulating TNF-α levels. Consistent with the lack of clinical benefit, enhanced markers of immune activation, frequency of cell subpopulations and aberrant cytokine profiles were not restored to normal levels by etanercept treatment. Remarkably, the levels of circulating TNF-α were significantly increased after treatment.

**Side effects of TNF-targeted therapy**

Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is a rare and devastating disease which results in death or an irreversible neurologic insult. Reactivation of JC virus is the cause of PML with death of oligodendrocytes resulting in demyelinating disease in the central nervous system. PML has occurred in lymphoproliferative disorders such as lymphoma, solid organ tumors, and bone marrow transplantation, and has classically occurred in profoundly immunosuppressed patients.

A surge in PML occurred in the 1980s with the onset of AIDS, highlighting the importance of T cells in the continued senescence of the JC virus in the human body. PML has also been described in patients with rheumatic diseases, including SLE, Wegener’s granulomatosis, systemic sclerosis, dermatomyositis, polymyositis, and RA.

The development of PML is either due to the immuno suppressive treatment, the disease itself, or both. Recently, biologic drugs including natalizumab for multiple sclerosis and rituximab for lymphoma and SLE have been associated with the development of PML. Not all biologic drugs increase the risk of PML development. No known cases of PML associated with TNF-targeted biologic drugs have been reported.

Two patients with SLE treated with immuno-suppression and rituximab developed PML. The manufacturer estimated that 10,000 SLE patients had received rituximab therapy. Although it seems convenient to blame the biologic agents alone, it is important to recall that PML has been reported in the literature without biologic therapies in 15 cases of non-SLE rheumatic diseases on immuno-suppression and 26 cases of SLE patients on immunosuppression.

Infections
Adverse events include infections e.g. activation of tuberculosis, pulmonary and disseminated histoplasmosis, coccidioidomycosis, blastomycosis and other opportunistic infections. In some patients, the diagnosis of histoplasmosis was initially unrecognised and antifungal treatment was delayed. Some of these patients died from histoplasmosis. There were also deaths in patients with coccidioidomycosis and blastomycosis.

The US Food and Drug Administration (FDA) has warned that for patients taking TNF blockers who present with signs and symptoms such as fever, malaise, weight loss, sweats, cough, dyspnea, and/or pulmonary infiltrates, or other serious systemic illness with or without concomitant shock, healthcare professionals should ascertain if patients live in or have traveled to areas of endemic mycoses.

Malignancies and cardiovascular disorders
An increased risk has been found for cancer, lymphoma, and cardiovascular disease.

Autoimmune diseases
There are a growing number of reports of the development of autoimmune processes related to TNF-targeted therapies, ranging from asymptomatic immunologic alterations to life-threatening systemic autoimmune diseases.113

A literature search by Ramos-Casals et al identified 233 cases of autoimmune diseases (vasculitis in 113, SLE in 92, interstitial lung diseases in 24, and other diseases in 4) secondary to TNF-targeted therapies in 226 patients.114 The anti-TNF agents were administered for rheumatoid arthritis (RA) in 187 patients, Crohn’s disease in 17, ankylosing spondylitis in 7, psoriatic arthritis in 6, juvenile RA in 5, and other diseases in 3. The anti-TNF agents administered were infliximab in 105 patients, etanercept in 96, adalimumab in 21, and other anti-TNF agents in 3.

In the patients who developed vasculitis, leukocytoclastic vasculitis was the most frequent type of vasculitis, and purpura was the most frequent cutaneous lesion. A significant finding was that one quarter of patients with vasculitis related to anti-TNF agents had extracutaneous involvement of the vasculitis.

In patients with interstitial lung disease, two specific characteristics should be highlighted: the poor prognosis in spite of cessation of anti-TNF therapy, and the possible adjuvant role of concomitant methotrexate.

In patients with preexisting autoimmune diseases such as SLE and/or vasculitis, anti-TNF agents should be used with caution, especially when renal, pulmonary, or neurologic involvement is demonstrated. Anti-TNF agents should not be used in patients with preexisting interstitial lung disorders.114

Conclusion on TNF-targeted therapy
More than a million patients have been treated with the 3 currently available anti-TNF agents for a variety of rheumatic, digestive, and dermatologic diseases. TNF-targeted therapies have been found very efficacious in controlling typical inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, Crohn’s disease and psoriasis. Unfortunately, this is not the case for Sjögren’s syndrome and SLE.

The use of anti-TNF agents has been associated with the development of autoimmune diseases such as cutaneous vasculitis, lupus-like syndrome, SLE, and

Serum sickness
Drugs that contain foreign (e.g. from the mouse) antibody fragments, such as infliximab and rituximab, initiate the formation of antibodies to these fragments.

This serum sickness reaction is the background of some of the side effects. The antibodies to these mouse fragments may also inactivate the drug. In clinical practice, the administration of these drugs is combined with some immunomodulating drug such as prednisolone or methotrexate to prevent the formation of antibodies to the drug.
interstitial lung disease. In patients with preexisting autoimmune diseases such as SLE, anti-TNF agents should be used with great caution, especially when renal, pulmonary, or neurologic involvement is demonstrated, and should not be used in patients with preexisting interstitial pulmonary disorders.\textsuperscript{114}

**IL-6 -targeted biologicals**

**Tocilizumab or atlizumab**

Tocilizumab or atlizumab is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R) used as an immunosuppressive drug, mainly for the treatment of rheumatoid arthritis. IL-6 is a cytokine that plays an important role in the immune response and is implicated in the pathogenesis of many diseases, such as autoimmune diseases, multiple myeloma and prostate cancer.

No data are available on therapy with this biological in Sjögren syndrome.

**Anti-B lymphocyte biologicals**

**Rituximab**

Rituximab (Mabthera\textsuperscript{®}, Rituxan\textsuperscript{®}) is a mouse-human chimeric antibody to the CD20 antigen. CD20 is a protein that is present on the surface of normal B-lymphocytes and almost all non-Hodgkin lymphomas. B cells are killed by the immune systems after binding of rituximab to the CD20 antigen on the cells. Rituximab has been shown to be effective in malignant diseases of B lymphocytes (B cell leukemia, B cell lymphoma) and rheumatoid arthritis. There is preliminary evidence for efficacy in many autoimmune diseases. Examples are autoimmune hemolytic anemia, pure red cell aplasia, idiopathic thrombocytopenic purpura, Evans syndrome, vasculitis, multiple sclerosis, pemphigus, pemphigoid, type 1 diabetes mellitus, SLE, and Sjögren’s syndrome.

**Studies in patients with Sjögren’s syndrome**

A small open-label study\textsuperscript{81} and several case reports\textsuperscript{82-91} are promising and suggest that rituximab may be effective in Sjögren’s patients with non-Hodgkin lymphoma and those with severe complications that do not respond to other treatments such as severe thrombocytopenia.

Yamout et al described a 47-year-old female with Sjögren’s syndrome and severe weakness in her legs due to myelitis. She had been initially treated with corticosteroids and intravenous cyclophosphamide with significant improvement but then deteriorated. The patient responded within a few days on a weekly dose of rituximab (375 mg/m\textsuperscript{2}) for four consecutive weeks and the improvement sustained at least eight months after her last dose.\textsuperscript{89}

A small double blind placebo-controlled study has shown that two infusions of rituximab 1 g (with oral and intravenous steroids to avoid serum sickness) significantly improved fatigue and social functioning six months later.\textsuperscript{92}

Depletion of peripheral B lymphocytes has been found to be complete 5 weeks after onset of therapy. By 36 weeks, B cell numbers had returned, although levels were still low in some patients. Stimulated salivary flow showed a significant increase at week 12, followed by a gradual decline to just above baseline at 48 weeks. Similarly, a significant improvement of most of the visual analogue scale (VAS) scores for dry mouth and most domains of the Multidimensional Fatigue Inventory (MFI, see explanation in chapter 6) was observed, followed by a gradual decline to near baseline.\textsuperscript{150}

Retreatment also had a significant effect on B cells, levels of IgM rheumatoid factor (RF) and stimulated salivary flow similar to the effects of the first course. VAS scores for dry mouth, MFI scores for general fatigue and SF-36 questionnaire scores for physical functioning improved significantly too.\textsuperscript{150}

Data suggest that rituximab is effective for at least 6-9 months in patients with primary Sjögren’s syndrome with active disease, improving subjective and objective symptoms. Retreatment resulted in a good clinical response.

**Side effects**

Mild side effects are common such as fever, chills, arthralgia, hypertension and infections. Serum sickness-like disease (purpura, arthralgia, myalgia) after rituximab infusion is not rare but may be reduced when higher doses of corticosteroids are given during treatment.\textsuperscript{150}

Severe or fatal side effects are rare and include severe mucosal reactions, progressive multifocal leukoencephalopathy (PML, see box), hepatitis B reactivation with fulminant hepatitis, other viral infections, cardiovascular events, renal toxicity, and bowel obstruction and perforation. Nearly two thirds of cases of PML in patients with rheumatic diseases reported in the medical literature occurred in patients with SLE. Over 40% of PML cases in SLE

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**Zumabs**
The suffix -zumab implies that the drug is a recombinant humanized monoclonal antibody.
occurred in patients who had had minimal iatrogenic immunosuppression, suggesting that SLE itself may predispose to PML.\textsuperscript{123} The occurrence of PML due to reactivation of JC virus infection leading to death 18 months after taking the last dose of rituximab in a patient with complicated RA, has resulted in an update of the package insert warning by the FDA.

This warning has previously noted reports of PML in patients with hematologic malignancies and autoimmune diseases for which rituximab is not approved. It has been updated to reflect the case of PML in an RA patient treated with rituximab (approved indication).

**Epratuzumab**

Epratuzumab is a recombinant humanised anti-CD22 monoclonal antibody. CD22 is a cell surface glycoprotein present on mature B-lymphocytes and on many types of malignant B-cells. Epratuzumab appears to function, in contrast to CD20 antibodies, more by modulation of B-cells than by their depletion capacity.

Steinfeld et al\textsuperscript{148} investigated the efficacy of epratuzumab in an open-label study in patients with active primary Sjögren’s syndrome. Sixteen patients received 4 infusions of 360 mg/m\(^2\) epratuzumab once every 2 weeks, with 6 months of follow-up. 53% to 67% achieved a clinical response at 6 and 32 weeks, respectively. According to the authors, epratuzumab is a promising therapy in active Sjögren’s syndrome, but further studies are needed.

**Belimumab**

Belimumab is a fully human IgG1 antibody directed against the B cell activating factor (BAFF) or B-lymphocyte stimulator (BlyS) protein. BlyS/BAFF is a TNF family member that supports B-lymphocyte maturation and survival. BlyS/BAFF has been implicated in the pathogenesis of autoimmune diseases and B-lymphocyte malignancies. Belimumab was developed to antagonize BlyS/BAFF activity in autoimmune diseases and B-lymphocyte malignancies.\textsuperscript{126} BlyS/BAFF is made in both membrane-bound and soluble forms by myeloid cells and dendritic cells, as well as by some T cells.

Recent studies describe a higher expression of BlyS/BAFF in patients with Sjögren’s syndrome.

Belimumab was well tolerated in treatment of RA over 24 weeks and SLE over 3 years. It significantly decreased rheumatoid factor (RF) levels, and modestly reduced symptoms of RA, especially in some subgroups such as patients with high disease activity, positive rheumatoid factor and no anti-TNF treatment experience. It also significantly reduced symptoms of SLE, and decreased anti-dsDNA autoantibodies during a long-period treatment.

BlyS/BAFF-blocking agents may thus also be a promising therapy for Sjögren’s syndrome.\textsuperscript{127}

According to clinical trial registries of the WHO and NIH (see box below) no clinical trials with belizumab are ongoing in patients with Sjögren’s syndrome to date (accessed 22 October 2008).

**Anti-T lymphocyte biologicals**

**Abatacept**

Abatacept (Orencia\textsuperscript{®}) is a fusion protein composed of an immunoglobulin fused to the extracellular domain of CTLA-4, a molecule capable of binding B7. It is licensed in the US for the treatment of rheumatoid arthritis in the case of inadequate response to anti-TNF-α therapy.

T cell activation requires two signals: binding of the T cell receptor to the antigen-MHC complex on the antigen presenting cell (APC) and a costimulatory signal provided by the binding of the T cell’s CD28 protein to the B7 protein on the APC. Abatacept, which contains a high-affinity binding site for B7, works by binding to the B7 protein on APCs and preventing them from delivering the costimulatory signal to T cells, thus preventing the full activation of T cells.

**Efalizumab**

Efalizumab was designed to treat psoriasis. It binds to the CD11a subunit of lymphocyte function-associated antigen 1 and acts as an immunosuppressant. It is administered once weekly by subcutaneous injection. It acts to inhibit white blood cell migration out of blood vessels into tissues. Known side effects included bacterial sepsis, viral meningitis, invasive fungal disease and PML (see previous page). Four cases of PML were reported in plaque psoriasis patients, an incidence of about one in 500 treated patients. It has been withdrawn from the market.

**Alefacept**

Alefacept (Amevive\textsuperscript{®}) is a fusion protein: it combines part of an antibody with a protein that blocks the growth of some types of T cells. Alefacept is used to control inflammation in moderate to severe psoriasis with plaque formation. It interferes with lymphocyte activation and is also being studied in the treatment of cutaneous T-cell lymphoma and T-cell non-Hodgkin lymphoma.

Alefacept inhibits the activation of CD4+ and CD8+ T cells by interfering with CD2 on the T cell membrane thereby blocking the costimulatory molecule LFA-3/CD2 interaction. It also induces apoptosis of memory-
References


77. See the website of the FDA for reports of the Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, 16-18 February 2005.


82. Shih WJ, Ghesani N, Hongming Z, et al. F-18 FDG positron emission tomography demonstrates resolution of non-


Latest additions or modifications (date: dd.mm.yyyy)

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<td>information added on chloroquine maculopathy only occurring in doses exceeding 6.5 mg/kg/day of HCQ</td>
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<td>Refs 173 and 174 added; need incorporation in the text Ref 175 added on new information on HCQ retinal toxicity and recommendations for early detection</td>
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