Prevalence of chronic ocular complications in Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

By

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University of Cape Town

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Preface

I hereby declare that this dissertation has been my own work and has not been submitted in any form to any other university. The research work was carried out in the Division of Ophthalmology, Groote Schuur Hospital, University of Cape Town, under the supervision of Dr Karin Lecuona.

Signed by candidate

signature removal

__24th____ Day of _____August_____ 2013

Acknowledgements:

This work in its entirety is dedicated to my loving wife, Nadia who stood by me in every aspect of my post graduate studies and this project. You were my pillar of strength during this time and I love you with all my heart.

Presentations of the results of this study:

- Department of Surgery, University of Cape Town faculty research day – 2010

- Ophthalmological Society of South Africa (OSSA) congress – Port Elizabeth, 2011

- Royal Australian and New Zealand College of Ophthalmology Congress- Hobart, Tasmania, 2013

Contents

Chapter 1

Study Protocol

Study Protocol

Title:

Prevalence of chronic ocular complications in Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

Research question:

What are the degrees of involvement and the long-term complications of Stevens–Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) on the different external ocular structures?

Investigators:

Dr Lourens van Zyl (Principle investigator)

Dr Karin Lecuona (Supervisor)

Abstract:

Objectives: The main objective of the study is to identify and grade the severity of chronic ocular complications in patients who were treated for SJS and TEN at Groote Schuur Hospital. The secondary objective is to identify patients who need referrals to specialist ophthalmic clinics for treatable ocular complications of SJS and TEN.

Design: The design of the study is a prospective cross-sectional study of consecutive patients treated at Groote Schuur Hospital for SJS and TEN.

Setting: Patients will be examined and data will be gathered in the Eye Clinic at Groote Schuur Hospital.

Study participants: Patients who were diagnosed with SJS or TEN and treated by the Department of Dermatology at Groote Schuur Hospital from 2003 to 2009.

Inclusion criteria:

- Patients with a dermatological diagnosis of SJS or TEN who were admitted and treated at Groote Schuur Hospital.
- Patients with a diagnosis of SJS or TEN for six months or longer.
- Both eyes of patients will be included, even if there is no clinical evidence of involvement, as it will form part of the statistics.

Exclusion criteria:

- Patients with previous eyelid or ocular surface surgery.
- Patients with a follow-up of less than six months.

Outcome measures:

The degree of involvement of the cornea, conjunctiva and eyelids will be assessed according to the following classifications:

1. Corneal

- superficial punctate keratopathy (SPK)
- epithelial defects
- loss of the palisades of Vogt (POV)
- conjunctivalisation
- neovascularisation
- opacification
- keratinisation

2. Conjunctiva

- hyperaemia
- symblepharon formation

3. Eyelid

- trichiasis
- mucocutaneous junction involvement
- meibomian gland involvement
- punctal damage.

Ocular abnormalities unrelated to ocular surface disorders will be recorded, including cataracts, glaucoma, retinal diseases and scleritis. Their presence, absence or inability to be diagnosed because of ocular surface abnormalities will be recorded.

Due to the high prevalence of HIV in our population, we will compare the ocular complications resulting from SJS and TEN on HIV-positive and HIV-negative patients.

The outcome measures will include:

- What percentage of patients have no external ocular involvement?
- What percentage of patients have external ocular involvement, and to what extent?
- What percentage of patients are legally blind (presenting visual acuity of less than 3/60 in the better eye) due to SJS and TEN?

Follow up: all patients with ocular involvement will be referred to appropriate specialist clinics for treatment. Minor abnormalities of treatable consequences will be referred to day hospitals for further treatment. All patients that are blind due to SJS or TEN will receive referrals to Social Services for disability grants and to the League of Friends of the Blind (LOFOB) for rehabilitation.

Specific aims:

The aim of the study is to identify the proportion of patients who have developed chronic ophthalmic complications due to SJS or TEN. Further, we want to grade the extent and severity of chronic ocular manifestations to better predict the visual prognosis and treatment needed for patients with ocular involvement. As there are no universal classifications of chronic ocular complications following SJS and TEN, previous studies cannot be compared. We aim to use the same classification in our study according to the latest published classification system.[1] The secondary aim is to identify treatable consequences that can prevent a severe decrease in vision.

Background and significance:

SJS and TEN is a complex immunological syndrome that is characterised by mucocutaneous blistering of the skin and at least two mucous membranes.[1,2,3] The so-called 'target lesions' and blistering of the skin are pathonomonic of the disease.[4] Mucosal blisters develop in the mouth and nose, and these usually rupture and form erosions. Haemorrhagic crusting of the lips is a characteristic sign, but genital involvement is more uncommon. Blistering is usually transient and may be widespread and associated with haemorrhage and necrosis. Healing occurs within four weeks, usually leaving a pigmented scar. Sloughing of the epidermis is widespread in TEN.[3,4]

SJS and TEN have the same signs and symptoms, but they differ in severity, with TEN involving blistering and sloughing of skin of more than 30% of the body's surface.

Males are affected more than females, and the disease can occur at any age.[4]

The disease is thought to be either a delayed hypersensitivity reaction to certain medications or a response to epithelial cell antigens modified by drug exposure.[3] Genetic predisposition may also play a part due to a genetically determined enzyme deficiency for the metabolites of certain medicines.[2] The medicines most commonly associated with SJS and TEN are antibiotics (especially trimetroprim), analgesics, cold remedies NSAIDs, phenytoin, allupurinol and acetazolamide.[1] In the past decade, anti-retroviral treatment

has surpassed most other medicines as the main culprit in the cause of SJS and TEN in developing countries.[4]

As symptoms develop up to three weeks after exposure, the precipitating cause cannot be identified with certainty in 50% of cases.[3]

It is reported that approximately 27–80% of hospitalised patients with SJS and TEN develop acute ocular complications.[1] Although severe corneal damage can result from the acute effects of the disease, corneal opacification usually results from chronic complications.[3] Corneal micro-trauma due to keratinisation of the eyelid margin and a variable degree of meibomian gland dysfunction are the main causes of a decrease in visual acuity.[2]

While the majority of patients have minimal long-term ocular involvement, it is known that some patients may present with severe ocular complications that result in visual impairment and blindness. The risk factors for poor outcomes are not known. It is thought that suppression of inflammation in the acute stage might reduce corneal damage scarring due to blink-related micro-trauma caused by conjunctival and tarsal scarring.[2,3]

Most studies about chronic ocular complications in SJS and TEN only include study subjects with known ocular involvement. In addition, most studies are retrospective and use a non-comparative grading system.

In this study, we will use a newly published grading system developed specifically to classify chronic ocular complications. This will be the first published study relating to ocular complications due to SJS and TEN in Africa.

Research Plan:

Patients who have a dermatological diagnosis with SJS or TEN will be identified and recruited from a database of patients provided by the Department of Dermatology at Groote Schuur Hospital. Only patients with a follow-up of more than six months after the onset of SJS or TEN will be included in the study. Identified patients will be contacted by the ward D4 secretary to follow up in either ward D4 or the ophthalmology out-patients department on a given date. Patients will be informed of the study and will need to sign consent forms for their data to be used in the study. A one-off

visit will be necessary to obtain all data. Study participants who had SJS or TEN between 2003 and 2009 will be recruited for the study.

The symptoms and ocular findings will be recorded on an itemised collection form. An assessment of the presenting and pinhole Snellen visual acuity will be performed. A slit lamp examination, including fluorescein staining, will be done on both eyes to examine the external ocular structures. Tonometry will be performed on all patients. Tear break-up time will be added to the measurements, and dry eye symptoms will be assessed.

Data obtained from the ocular examination will be divided into complications of the eyelids, conjunctiva and cornea, and the data will be recorded on the itemised patient chart. The disease severity will include 13 components that are graded on a scale of 0 to 3 to give an overall score from 0 to 39, with 39 representing the most severely affected eyes. Data for patients without ocular involvement will also be recorded.

Drug history, HIV status and CD4 will be obtained from the dermatology records. A drug will be considered a possible etiological agent if it has been taken within two weeks of the onset of disease.

Patients requiring further referrals will be referred to the appropriate specialist clinic (e.g. cornea clinic) or day hospital.

Data will be captured in a Microsoft Excel spreadsheet and analysed using Stata. Patient characteristics and ophthalmological characteristics with means and median properties will be analysed using with a T-test and properties with a chi^2 test.

Photographs will be taken for publication purposes. Photos will only be taken of patients' eyes and the anterior structures in order to protect patients' identities. No names will be used in the study; only hospital numbers will be used to identify patients.

Ethics:

Ethical approval will be obtained from the University of Cape Town Faculty of Health Sciences Ethics Committee.

Reporting:

A paper reporting the findings of the study will be submitted to a peer-reviewed journal for consideration for publication.

Logistics

Timetable

Activity	M 09	J	J	A	S	O	N	D
Preparation of protocol	X							
Ethical approval	X	X						
Pilot study			X					
Data collection				X	X	X		
Data analysis							X	
Write up								X

Discomforts and risks:

Patients may be inconvenienced. A one-off 20-minute examination will be necessary to capture the data. The only discomfort that was identified might be the travel to the hospital; in the case of the visually impaired, an escort might be needed. Visits will be charged according to the UPFS. As most patients who are treated for TENS and SJS at Groote Schuur Hospital are classified as H1, they will not be required to pay for the clinic visit. We intend to compensate each patient with R150 to cover travel expenses. A budget of R7500 will be required, and funding will be obtained from the University of Cape Town Research Fund. Files will be gathered from the records department, and patients will be informed to attend at either D4 or the Ophthalmology out-patients department.

Benefits:

- Identify and grade the long-term complications of SJS and TEN.
- Identify the risk of developing ophthalmic complications if a patient suffers from SJS or TEN.
- Identify patients who will benefit from any secondary intervention to improve their current visual acuity.
- Refer patients to appropriate specialist clinics or day hospitals where required.

Financial risks:

Participants will not incur any financial risk.

Financial benefits:

We intend to compensate each participant for their travel expenses, as this study is not part of the standard care of the participants. Patients will be paid a fee to travel to and from the hospital. An amount of R150 per patient is required and, in the case of a patient travelling from outside the metro pole of

Cape Town, an amount of R200 is required. We wish to obtain sponsorship from the University of Cape Town research grants.

Conflict of interest:

There is no conflict of interest. No authors have made a financial gain from this study.

Literature

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Chapter 2

Literature review

Literature Review

Introduction

The objective of the literature review is to examine whether sufficient literature has been published on the incidence of chronic complications of Stevens–Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), as there has been an increase in the number of patients who present late with ocular complications secondary to SJS and TEN.

Another objective is to gather information on the chronic ocular complications of SJS or TEN. Specifically, I will examine the chronic complications; most patients are referred to the Ophthalmology Department several months after they have been treated for SJS or TEN. Long after the dermatological disease has ceased, these patients present mainly with chronic complications. Thus, I will examine the natural history of the disease in the chronic stages.

Further, I will observe whether there is a difference in the prevalence and severity of the eye disease in a setting where most of the patients are HIV-positive, compared to studies conducted in countries with a low prevalence of HIV.

I will examine studies and whether their classification systems can be used in a comparative study in an African setting, as there is no universal classification system of ocular complications in SJS and TEN.

Method:

A Pub-Med search was conducted using the Pub-Med search engine.

The keywords used were: chronic-eye-complications Stevens–Johnson syndrome Toxic epidermal necrolysis. Acronyms such as SJS and TEN and synonyms such as 'ocular' and 'long term' were used. A result with Erythema Multiforme (EM) was not used because it was regarded as a separate disease entity. The inclusion criteria were that the publication must only contain literature on chronic complications. Only English language articles were used and, where an article was not in English, the translated abstract was used.

Results:

The article that I found most relevant was by Sotozono et al. The paper evaluates the extent of chronic ocular manifestations after SJS and TEN, and it proposes a new grading system for the complications.[1] The study was conducted between 2003 and 2005, and it was a prospective multicentre case series done at three ophthalmic centres in Japan. Seventy-three patients (138 eyes) were included in the study. They were referred with a confirmed diagnosis of SJS or TEN and had a confirmed history of chronic ocular disease for more than one year. Patients were excluded if they had undergone any ocular surface surgery in the past. All data and medical histories were captured on an itemised data collection form. The main outcome measures were broadly classified as corneal, conjunctival and eyelid complications. Thirteen components were graded from 0 to 3 depending on the severity of the complication, where 0 is equal to no involvement and 3 is severe involvement.

The most commonly occurring complication was loss of the palisades of Vogt (POV) (114-eyes/82.6%). The second most common component was meibomian gland involvement (102 eyes/73.9%). The visual acuity in 53% of the study subjects was worse than 20/200. The severity of visual loss correlated with the severity of the corneal, eyelid and conjunctival involvement. Eyes with a higher total score for the three complications had poorer vision ($p<0.0001$). Multivariate regression analysis showed that corneal neovascularisation ($p<0.0001$), opacification ($p<0.0001$), keratinisation ($p<0.0142$) and cataracts ($p<0.0375$) significantly affected log MAR acuities. The authors describe a new grading system for the extent and severity of ocular involvement and conclude that it correlates significantly with the final visual outcome.

This was the only prospective study conducted on patients with SJS and TEN with chronic ocular complications.

One of the limitations of this study was that dry eye syndrome was not part of the classification system; whereas most other studies in the literature review included dry eye symptoms. In my experience, most patients presenting in the late stages have dry eye syndrome. This complication is caused by the known

fact that SJS/TEN destroys conjunctival goblet cells. These cells are important in the production of the mucus layer in the tear film, and they cause an evaporative type of dry eye syndrome. I included dry eye symptoms and added tear break-up time to the data collection form to be more comparable with other studies.

Similar to my study, De Rojas and others from the Moorfields Cornea and External diseases service in London reported on the natural history of SJS and TEN, and they characterised patterns of chronic ocular disease.[2] The study was a retrospective case study of 30 patients (60 eyes) between 1975 and 2004. A limitation of this study was that data were collected from case notes retrospectively. All patients had a dermatological diagnosis of SJS and TEN. The principle outcome measure of the study was to identify and classify the patterns in chronic eye disease in SJS and TEN. The authors grouped the patterns of chronic ocular complications as follows:

- Mild to moderate involvement: eyes with mild to moderate complications due to conjunctival scarring. These eyes have healthy corneas with no recurrent or progressive inflammation.
- Severe involvement: eyes with severe complications resulting mainly from conjunctival scarring. There was no evidence of stem cell deficiency. These eyes were very dry with an opaque, vascularised and irregular surface. They had a stable epithelium and no evidence of conjunctival inflammation or progressive scarring.
- Ocular surface disease: surface failure with evidence of stem cell deficiency occurring after the acute attack of SJS.
- Recurrent inflammation: eyes with recurrent episodes of conjunctival inflammation without progressive scarring.
- Scleritis: patients developing scleritis after the acute attack.
- Mucus membrane pemphigoid: eyes with early or late conjunctival inflammation and leading to progressive scarring.

The authors conclude that ocular disease following SJS and TEN is not limited to the complications of the acute phase illness, and that

ophthalmologists need to be aware of disease progression. Successful management of chronic ocular complications in SJS and TEN requires the identification of the different components of the disease for the prognosis of vision. Although this was a retrospective study, this conclusion confirmed what we were seeing clinically in the Outpatients department; namely, that patients with minimal ocular involvement in the acute phase presented with chronic ocular complications more than six months later.

SJS and TEN as a disease entity itself does not cause visual loss; however, patients can present with severe visual loss and morbidity due to the dermatological disease. Di Pascuale examined the correlation of corneal complications secondary to cicatricial eyelid pathologies in SJS and TEN.[3] The study was a retrospective observational case study of 38 patients between 2002 and 2004 who had confirmed SJS or TEN. The inclusion criteria was known ocular complications from SJS and TEN, and the exclusion criterion was any ocular surface surgery before or after the acute attack. The main outcome measures were: floppy eyelids (graded as 1–3 depending on the severity) and cicatricial complications involving different locations of the ocular surface, such as lids (entropion), puncta (auto occlusion), lashes (trichiasis and districhiasis), lid margin (scar and keratinisation), meibomian gland metaplasia, symblepharon and bulbar conjuntiva (scarring with or without motility restriction). The severity of the cicatricial lid margin and tarsal pathologies was graded as mild, moderate or severe by reviewing photographs of the study participants. The corneal complications were also graded as mild (clear cornea with superficial punctate keratopathy (SPK)), moderate (corneal haze and peripheral corneal neovascularisation) and severe (central corneal haze or scarring with extensive neovascularisation). In all of the cases reviewed, keratinisation of the eyelids with meibomian dysfunction was observed. Floppy eyelids (95% confidence intervals (CIs), p=0.5), trichiasis (95% CI, p=0.2), partially occluded lacrimal puncta (95%, p=0.9), symblepharon (95%, p=0.5) and tear deficiency (95% CI, p=0.5) were not significantly correlated with corneal complications. However, there was a strong correlation between the extent of corneal complications and the eyelid margin and tarsal pathology (95% CI, p=0.006). The authors concluded that lid margin keratinisation and tarsal scarring with tear deficiency contribute to

corneal complications because of blink-related micro-trauma. In addition, SJS and TEN do not directly cause visual impairment; rather, it is due to the chronic complications of the disease. Although this was a retrospective study, it was useful because the authors studied photographs of patients' pathology to gather data. The data were therefore highly objective and reproducible.

Kompella and others also examined ocular complications, aetiological factors and the management of these complications in patients with SJS.[4] The retrospective study was conducted at a tertiary institution in India by reviewing the medical records of patients seen between 1987 and 1998. The details of the ocular exams were collected to determine a pattern of presentation, complications, treatment responses and outcomes. The ocular findings were divided into those involving eyelids, conjunctiva and cornea. Lid abnormalities included lid thickening, discharge, meibonitis, blepharitis, trichiasis, dystrichiasis, entropion, ectropion. Conjunctival pathologies included congestion, xerosis, symblepharon and ankyloblepharon. Corneal abnormalities included SPK, thinning, scarring, vascularisation, keratinisation and infectious keratitis. All 95 participants had bilateral and symmetric disease. The average time of presentation to the Institute was one year after the acute phase. Lid abnormalities were observed in 91.5% of patients, while 96.8% had conjunctival abnormalities and 97.8% had corneal complications. A best-corrected visual acuity of 6/12 or better was reported in 33.6% of patients, while 17% had acuity between 6/12 and 6/60, and 41.05% had a visual acuity of 6/60 or less. The authors concluded that SJS and TEN is an important cause of ocular morbidity and visual loss, which affect the quality of life. The authors pointed out that few treatment options were available for chronic complications, and that advances in immune modulation techniques are required to prevent many chronic complications.

Yip and others also tried to identify predictors for the development of late complications in a study conducted in Singapore.[5] They noted that most studies on ocular complications due to SJS and TEN were conducted on Caucasian patients. They stated that there are genetic differences in drug metabolism, and that the severity of the disease on the eyes may be different in the South East Asian population. Yip set out to establish if there was a difference in the frequency and severity of ocular complications between

Caucasian and Asian patients—both acutely and in the long term. The study was a retrospective case study of 117 patients. Only 44 had a follow up of six months; thus, the chronic complications were only described in 44 patients. The cases of patients seen between 1993 and 2002 were reviewed, and only patients with known ocular involvement were included. Patients with a minimum of six months follow-up were reviewed for late complications. Ocular involvement was defined as mild, moderate and severe. Mild involvement consisted of lid oedema and/or mild conjunctival injection and/or chemosis only. Moderate involvement comprised membranous conjunctivitis and/or corneal epithelial defects and/or corneal ulceration and/or corneal infiltrates. Severe involvement comprised symblepharon formation and/or non-healing corneal epithelial defects and/or visual loss and/or conjunctival fornix shortening. The most common chronic complication was dry eye syndrome and trichiasis. Therefore, I included dry eye symptoms as an outcome measure in my study.

The authors found that patients treated with topical antibiotics were likely to develop chronic complications—especially dry eyes. They found no difference between the acute eye involvement and late complications between patients with SJS and TEN. Similar to other authors, they concluded that the severity of acute ocular involvement in SJS and TEN does not predict late complications. They further concluded that early intervention might prevent chronic complications from affecting the external ocular structures.

Gueudry and others also examined risk factors and predictors for developing late ocular complications in SJS and TEN[6] in a retrospective study conducted in France on patients seen between 1994 and 2002. There were 117 patients, of whom 49 had chronic ocular involvement due to SJS or TEN. They described the acute and late ocular manifestations as mild, moderate and severe. Mild ocular involvement consisted of eyelid oedema and/or mild conjunctival injection and/or chemosis only. Moderate involvement consisted of membranous conjunctivitis and/or corneal epithelial defects, with more than 30% healing with medical treatment and/or corneal ulceration and/or corneal infiltrates. Severe involvement consisted of symblepharon formation and/or non-healing corneal epithelial defects and/or visual loss and/or conjunctival fornix shortening. Each patient had an ophthalmic examination and had to

complete an ocular surface disease index (OSDI) questionnaire to determine the extent of his or her chronic ocular symptoms. The OSDI questionnaire was used to ascertain the severity of dry eye syndrome. This was used by the authors following reports that patients who suffered from SJS or TEN had dry eye syndrome as a chronic complication of the disease. This further strengthened my decision to add dry eyes to my study. There were 129 patients with acute involvement of their eyes, and 61 of these patients completed the OSDI questionnaire. Of these 61 patients, 49 had an ophthalmic examination, which provided data for the study. Dry eye syndrome and subconjunctival fibrosis were the most common chronic complications. Even patients without acute ocular involvement developed dry eye syndrome. The authors concluded that all patients with SJS and TEN should receive an initial ophthalmological assessment, and that these patients require close follow-up. They also stated that ocular medications with preservatives should be avoided, as preservatives are known to cause ocular surface disease, which can worsen the chronic ocular complications of SJS and TEN.

In a related article, Yip showed that, despite highly sophisticated interventions, patients develop chronic ocular involvement in SJS and TEN regardless of whether they are treated in the acute stage.[7] This was a small retrospective study of 10 patients that compared the outcomes of patients receiving high-dose intravenous immuno-globulin with those who did not. The study concluded that high-dose intravenous immuno-globulin did not seem to reduce the severity of visually significant ocular complications in patients with SJS and TEN.

The previous three articles prove that acute complications, or a lack thereof, are not predictors of the severity of chronic ocular complications. The authors recommended that patients with SJS or TEN, regardless of the treatment in the acute phase, should be followed-up closely, as there is a high likelihood of developing chronic ocular complications.

In contrast to the previous three studies, a case study of three child patients with SJS and TEN with acute and chronic ocular complications was presented by Gotz-Wieckowska.[8] The children were aged between six and 12 years. Two of the cases received early ophthalmological intervention by giving the children symblepharon massages, steroids and artificial tears. According to

the authors, the outcomes of the treatments were excellent. In the latter case, where the child did not receive early ophthalmological intervention, the patient developed severe chronic ocular disease. This included ocular surface neovascularisation and posterior lid keratinisation. According to the authors, the results of the treatment were not satisfactory. The authors concluded that early intervention in children with SJS and TEN may prevent chronic ocular surface complications. Even though this is a small comparative case study, it highlights the need for a study to examine the natural history and progression of acute ocular complications into chronic complications.

Due to the high prevalence of HIV infection in South Africa and recent reports of the high numbers of SJS and TEN due to Nevirapine and Co-trimoxasole, I found it relevant to search for the ocular complications of patients with AIDS who had SJS and TEN. There is little literature on the subject, and the only relevant article was by Belfort in 1991, who presented a case report on one patient with AIDS and TEN, and two patients with AIDS and SJS.[9] The patients developed severe dry eye symptoms, which were exacerbated by HIV-related lacrimal gland dysfunction. They were initially misdiagnosed as severe infectious kerato-conjunctivitis. The authors concluded that all cicatrising muco-cutaneous reactions should be treated correctly, and that patients with dry eyes should be treated to control chronic complications. It is not surprising that a condition that causes ocular mucous membrane damage, such as SJS and TEN, can exacerbate dry eye symptoms in HIV/AIDS, which in itself causes dry eye syndrome.

In conclusion, very few studies focus solely on chronic ocular complications and the incidence thereof in SJS and TEN. All of the above studies described patients with confirmed ocular disease. Patients were seen and treated by ophthalmologists before participating in the studies. None of the studies took a sample of patients with SJS and TEN, with or without confirmed ocular disease, to describe the prevalence of ocular surface disease after the dermatological lesions have healed.

There is a need to identify patients from the onset of SJS and TEN and to document and follow-up with these patients to monitor ocular complications. This would create a better understanding of the natural history of the disease and its ocular complications.

A limitation in the current literature is that no studies have been conducted in Africa. As Yip postulated that there might be differences in the severity of ocular disease in different races, it is important to conduct a study on African patients to assess the severity of ocular complications.

There does not appear to be a universal system of grading the chronic complications of SJS and TEN, and each author used his or her own classification. The adoption of a universal classification will bring it into line with other disease entities that have an internationally recognised classification system. This will better predict the visual prognosis and type of treatment that the patient might require. Further, it will be easier to compare outcomes in different studies.

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5. Sotozono C, Ang LP, Koizumi N, Higashihara H, Ueta M et al. New grading system for the evaluation of chronic ocular manifestations in patients with Stevens–Johnson syndrome. Ophthalmology 2007 Jul; **114**(7): 1294–302-12.

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Chapter 3

Manuscript

- 1. Author's guidelines, British Journal of Ophthalmology
- 2. Original article
- 3. Graphs and Tables

Manuscript

1. Author's guidelines, British Journal of Ophthalmology

British Journal of
OPHTHALMOLOGY

The word count excludes the title page, abstract, tables, acknowledgements and contributions and the references.

CANCER CLASSIFICATION SCHEME

Authors should use the American Joint Commission on Cancer classification scheme when describing patients with ophthalmic malignancies; see American Joint Committee on Cancer. JCC Cancer Staging Manual, Seventh Edition, Springer, New York.

Editorials

Timely succinct commentary on any aspect of clinical or laboratory ophthalmology, usually in relation to the subject matter of a paper to be published in the same issue. All editorials are commissioned.

1500 words, up to 2 images and tables, 25 references.

Original articles

Clinical Science: up to 2500 words, 5 images and tables, 25 references Laboratory Science: up to 2500 words, up to 5 images and tables, 25 references

Editors may request authors to shorten a submitted manuscript when in the opinion of the Editorial Board, the content does not justify the length. All types of original article should include the following.

Title Keywords (up to four) Addresses and which author address for correspondence Structured abstract: (200 words, headings: "Background/aims", "Methods", "Results", and "Conclusion") Introduction Materials and methods Results Discussion References and acknowledgements Legends for display items (Figures and Tables)

All original articles are subject to peer review and editorial approval.

Review articles

Review articles will address any aspect of clinical or laboratory ophthalmology. Most review articles are commissioned but uninvited reviews are also welcome. Prior discussion with the Editor is recommended.

Unstructured abstract: up to 200 words. Word count: up to 3000 words Tables/illustrations: up to 5 images and tables References: up to 100 references

All review articles are subject to peer review and editorial approval.

Global issues

Global issues paper emphasise epidemiology and public health issues especially from the underdeveloped countries.

Summary: should not exceed 200 words. 2000 words, up to 5 images and tables, 25 references. All global issues articles are subject to peer review and editorial approval.

Innovations

Manuscripts submitted in this category should describe innovative techniques in any field of ophthalmology including ophthalmic surgery, drugs, optics, and devices. Any relevant preclinical and clinical data should be included. The chief criterion for publication will be the novelty of concepts involved and potential for clinical applications.

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Education

Manuscripts submitted in this category emphasize clinically relevant management issues that help educate by increasing awareness (how it happened), provide practical guidance for performing common procedures and eliciting clinical signs (how to do it*), practical tips for interpreting test results (how to interpret), and provide simple explanations of how ophthalmic instruments and medications work (how it works). The chief criterion for publication will be educational value of the manuscript.

How it happened How to do it How to interpret How it works

1000 words, up to 2 images and tables, 15 references.

The manuscript should be divided into three parts (introduction/case report, 3 questions/answers, and discussion). The case report+ should describe exactly how it happened including any errors of judgement in management or diagnosis so that it can be a learning experience to the reader. The questions should be very specific, central to the theme of the report, and their answers form the essential educational component of the manuscript. Discussion should highlight additional related management (How it happened/ How to do it) or technical (How to interpret/How it works) aspects. A sample format can be downloaded here.

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+A completed patient consent form for case reports should be provided in all cases.

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300 words and 5 references

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2. Original article

Prevalence of chronic ocular complications in Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

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Keywords: Stevens–Johnson syndrome, Toxic Epidermal Necrolysis, chronic, ocular complications
Word count: 2220

Purpose: The objective of the study is to identify and grade the severity of chronic ocular complications in patients who suffered from Stevens–Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) and were treated at Groote Schuur Hospital in Cape Town, South Africa.

Design: Prospective cross-sectional study.

Method: A cohort of 52 consecutive patients (104 eyes) with a confirmed dermatological diagnosis of SJS or TEN for six months or longer was examined. The ocular complications were broadly classified into corneal, eyelid and conjunctival complications according to Sotozono's proposed classification system. The complications were graded from 0 to 3 depending on the severity.

Main Outcome Measures: These were classified into:
1. Corneal complications (superficial punctate keratopathy, epithelial defects, loss of the palisades of Vogt (POV), conjunctivalisation, neovascularisation, opacification and keratinisation)
2. Eyelid complications (trichiasis, mucocutaneous junction involvement, meibomian gland involvement, punctal damage)
3. Conjunctival complications (hyperaemia, symblepharon formation).

Results: A total of 108 eyes of 54 patients were included in the study. There were 28 males and 26 females. Medications caused SJS or TEN in all cases, and the most common associated drugs were: antibiotics (28%), anti-retroviral (34%) and anti-epileptic (22%) medications. Almost 60% (59.3%) of patients were HIV-positive, with CD4 counts ranging from six to 521 at the time of the dermatological diagnosis. Although only 11% of patients with SJS or TEN had acute ocular complications during the initial illness, 89% developed chronic ocular complications. Loss of the Pallisades of Vogt (POV) (85.2% (95% confidence intervals (CIs) 75.4–95.0%)) was the most common corneal complication, followed by superficial punctate keratopathy (SPK) of the corneal surface (40.7% (27.2–54.3%)). Among the six components of conjunctival and eyelid complications, a mild irregularity of the mucocutaneous junction abnormalities (79.6% (CI 68.5–90.7)) was the most

common, followed by mild conjunctival hyperaemia. There was no statistically significant difference in the severity of chronic ocular complications between HIV-positive and HIV-negative patients (p=0.4). In addition, the severity of chronic ocular complications was not statistically significantly associated with visual acuity loss (p=0.3).

Conclusion: We conclude that almost 90% of patients who are diagnosed with SJS or TEN will develop chronic ocular complications. Unless eyelids are severely affected, most chronic complications are mild to moderate ocular surface abnormalities and not necessarily vision-threatening complications.

Introduction

Stevens–Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are complex immunological syndromes that is characterised by mucocutaneous blistering of the skin and at least two mucous membranes.[1,2] Both are part of the same disease entity and differ only in severity. A typical lesion has the appearance of a target; this is considered pathognomonic. Males are affected more than females, and it can occur at any age.[3,4] The disease is thought to be either a delayed hypersensitivity reaction to certain medications or a response to epithelial cell antigens modified by drug exposure.[3,4] Genetic predisposition may also play a part due to a genetically determined enzyme deficiency for the metabolites of certain medicines.[2,3,5]

According to certain studies, 27–80% of cases progress to severe ocular disease during the acute dermatological disease. Ocular complications of SJS and TEN during the acute phase include conjunctival chemosis, conjunctival and corneal epithelial defects, corneal ulceration, corneal perforation, endophthalmitis and membrane formation.

It is not clear whether early intervention in the acute stages of SJS and TEN will limit ocular complications in future. Further, it is not known why patients who have no ocular involvement in the acute stages of SJS or TEN develop chronic ocular complications after the dermatological disease has ceased. Treatment of acute ocular manifestations usually begins with aggressive lubrication of the ocular surface. Most ophthalmologists use topical steroids, antibiotics and symblepharon lysis as inflammation and cicatricial changes ensue.[6]

The aim of the study is to identify the proportion of patients who develop long-term ophthalmic complications regardless of acute ocular involvement and treatment. The study was conducted at Groote Schuur Hospital in Cape Town, South Africa. Most of the study participants were indigenous black African and mixed-race patients, and most came from areas in Cape Town with low socio-economic circumstances and a high prevalence of HIV. No other studies have compared chronic ocular complications on HIV-positive

and HIV-negative patients resulting from SJS and TEN. The aim was to see if HIV infection affects the long-term outcomes of ocular complications resulting from SJS and TEN.

The extent and severity of chronic ocular manifestations were graded. Clinical involvements of the external ocular structures were graded according to the new grading system formulated by Sotozono et al.

Methods

Patients with a confirmed dermatological diagnosis of SJS and TEN were recruited from a database from the Department of Dermatology at Groote Schuur Hospital. A total of 54 consecutive living patients diagnosed between January 2003 and November 2009 were recruited for the study.

Participants included patients with a dermatological diagnosis of SJS or TEN that were admitted and treated for their dermatological disease at Groote Schuur Hospital with a follow-up of six months or longer. In addition, both eyes of patients were included, even if there was no clinical evidence of involvement. Patients were excluded if they had any previous eyelid or ocular surface surgery or refused recruitment.

Ethical approval was granted by the University of Cape Town Faculty of Health Sciences Ethics Committee.

The medical history, ophthalmic examination findings, HIV status and CD4 count of each patient, as well as their medical history, was captured on an itemised data collection form. The degree of involvement was classified into 13 components of three categories: Corneal (Table 1), Conjunctival and Eyelid complications (Table 2).

A score of 0 to 3 reflected increasing severity, with 0 representing no involvement (Table 3 and Table 4).
Tear break-up times were measured for each eye, and the tear film stability was assessed. Each eye was graded, and a score representing the total of

the sub-scores was assigned. This severity score could therefore range from 0 to 39, with 39 representing the worst affected.

Data were analysed using Stata version 11.1 (StataCorp LP, 4905 Lakeway Drive College Station, TX 77845 USA). Normality of the data was estimated using the Shapiro–Wilk Test. Medians, ranges and interquartile ranges (IQR) were estimated for non-normally distributed variables. Proportions and 95% confidence intervals (CIs) were estimated adjusting for clustering by patient where both eyes were analysed. The non-parametric Wilcoxon rank sum (Mann–Whitney) test was used to compare two medians, and the Kruskal–Wallis test was used when three or more medians were compared, because the data for eyes were clustered by patients. Somers-D p-values were used. The non-parametric Spearman's correlation coefficient was used to estimate the relationship between two scores.

Results

A total of 108 eyes of 54 patients were included in the study. There were 28 males and 26 females. The median age at diagnosis was 37 years and ranged between 12 and 74 years, the IQR was 26 to 47 (Graph 1). Medications were the cause in all cases. The most common associated drugs were: antibiotics (28%), anti-retroviral (34%) and anti-epileptic (22%) medications. Thirty-two (59.3%) patients were HIV-positive, with CD4 counts ranging between six and 521 (median 171.5 and IQR of 112–202) at the time of dermatological diagnosis.

Only six patients (11%) needed initial consultation and treatment by an ophthalmologist in the acute phase because of epithelial or conjunctival defects. However, six months or more after the initial presentation, 46 (85.2%) patients had developed chronic ocular complications.

Of the seven components of corneal complications, the loss of Pallisades of Vogt (POV) was the most common (85.2% (95%CI 75.4–95.0)). In most cases, loss of more than half of the circumference of the POV were noted. Superficial punctate keratopathy (SPK) was present in 81.2% of cases, and could most likely be attributed to the instability of the tear film.

Among the six components of conjunctival and eyelid complications, mild mucocutaneous junction abnormalities were the most common, with 79.6% (95%CI 68.5–90.7) of patients affected, followed by mild conjunctival hyperaemia at 40.7% (95%CI 31.5–50.6). Nine patients (17%) in the cohort had moderate to severe lid complications, which included trichiasis and mucocutaneous junction abnormalities. These patients' severity scores ranged between 19 and 29 and were the worst affected visually, with visual acuities ranging from 6/24 to counting fingers. These nine patients had extensive corneal opacification, which accounted for the low final visual aquity. Even though there was no statistically significant (p= 0.07, Spearman's rho=0.8) correlation between the extent of corneal complications and the eyelid abnormalities, there was clinical significance between the extent of eyelid complications and corneal opacification.

The overall severity scores ranged between 0 and 29, the median score was 9 and the IQR was 2.0–12.5. Despite the high percentage of chronic ocular complications, most patients had good visual acuities ranging from 6/6 to 6/18, with an average visual acuity of 6/13.4. The average visual acuity of the six patients who were assessed by an ophthalmologist for their acute ocular complications was 6/12.1. The average visual acuity of the patients who were not assessed by an ophthalmologist in the acute stages was 6/11.4 and was not statistically significant (p=0.045).

The severity scores were worse in females compared with males (medians and IQRs 3.5 (2.0–8.0) compared with 4.5 (3.0–11.0) respectively (Graph 2), but these differences were not statistically significant (Wilcoxon rank sum test z=-2.33, Somers-D p=0.09).

There was no statistically significant difference between severity scores between HIV-positive and HIV-negative patients (Wilcoxon rank sum test z=-0.87, Somers-D p=0.54). Further, by restricting the analysis to only HIV-infected patients, no statistically significant difference was found in severity scores by CD4 category (<200, 200–349, 350+, Kruskal–Wallis chi-squared test=1.09 with 2 d.f. Somers-D p=0.4). (Graph 3)

Discussion

External ocular complications due to SJS and TEN are associated with severe visual morbidity. Around 27–80% of hospitalised patients with SJS and TEN develop acute ocular complications.[1,2] According to De Rojas, chronic complications occur in 35% of patients with SJS and TEN.[2] There has been no standardised method for the classification of chronic complications of SJS and TEN, and each publication in the literature used its own classification system. This might have led to an under-estimation of true chronic complications, as almost 90% of patients examined in our study had chronic complications. We found the classification used by Sotozono useful in the analysis of our results. However, we added tear break-up time to the classification for comparison with other studies.[3,4,5,7]

This study confirmed previous findings that the severity of acute external ocular complications does not predict chronic complications.[5,8] Of the 11% of patients in our study that had an initial ophthalmological assessment, all had chronic complications but were not necessarily the worst affected of all participants. Our study thus confirms that acute ocular involvement may give rise to significant chronic complications, but it should only be regarded as a risk factor.

All patients received preserved lubrication during the acute phase of their treatment. It is possible that preservatives may cause ocular surface damage and consequently may have increased the incidence of chronic complications.[7]

This is the first study of its kind that has compared the outcomes of patients who were HIV-positive and HIV-negative in Africa. As HIV-positive patients have a high prevalence of dry eye syndrome, it was not surprising that 81% of patients in this study had SPK secondary to tear film instability. This proportion was higher than previously reported.[5,7] We found there was no

statistically significant difference between tear break-up times between HIV-positive and HIV-negative patients (p=0.98).

The management of chronic ocular complications due to SJS and TEN should be directed at minimising ocular surface inflammation.[2] The visual rehabilitation in patients with severe ocular involvement resulting from chronic complications is difficult and often frustrating for both the patient and the ophthalmologist.

The study has several weaknesses. Only 54 patients were recruited for the study. Several patients were deceased or were not contactable, which might have caused a gross underestimation of complications.
The fact that patients were seen prospectively and the data were not collected from case notes makes the recording of data objective and more accurate. All patients that were examined were seen by only one ophthalmologist to standardise the recording of the chronic complications. However, this is one of the largest series of its kind at a single unit.

We suggest that all patients with SJS and TEN should be on long-term lubrication, as most will suffer from dry eye syndrome. All patients should have an ophthalmological assessment to initiate chronic medication if indicated; however, unless eyelids are severely damaged, specialist ophthalmological intervention is unnecessary. Eyelid damage causes corneal opacification and is the main cause of visual acuity loss. Further, a standardised classification system should be adopted for clinical use and to standardise future studies. Continued research is necessary into treatment of the acute stages of the disease to prevent long-term complications.

We conclude that most patients will suffer from a wide variety of chronic ocular complications following SJS and TEN. Most complications are ocular surface abnormalities and not necessarily vision-threatening complications. The loss of Vogt's palisades and dry eye syndrome with SPK were the most common complications. Poorer visual outcomes can be expected if there are severe eyelid complications. HIV status and low CD4 count was not a risk

factor for more severe outcomes. All patients with SJS or TEN should have an ophthalmological evaluation regardless of initial non-ocular involvement.

Literature

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3. Graphs and Tables

Table 1.

Corneal complications:

Severity of superficial punctuate keratopathy

1= Staining of less than a $^1/_3$ of the corneal surface,

2= Staining of more than a $^1/_3$ but less than $^2/_3$ of corneal surface

3= Staining of more than $^2/_3$ of the corneal surface

Corneal epithelial defect:

1= Epithelial defect involving less than ¼ of the corneal surface

2= Epithelial defect involving more than ¼ but less than ½ of the corneal surface

3= Epithelial defect involving more than ½ of the corneal surface

Loss of the palisades of Vogt (POV):

1= Loss of less than ½ of the circumference of the POV,

2= Loss of more than ½ of the circumference of the POV

3=Total loss of the circumference of the POV

Conjunctivalisation:

1= Conjunctivalisation involving less than ¼ of the corneal surface

2= Conjunctivalisation involving more than ¼ but less than ½ of the corneal surface

3= Conjunctivalisation involving more than ½ of the corneal surface

Corneal neovascularisation:

1= Neovascularisation confined to the corneal periphery

2= Neovascularisation extending up to the pupil margin

3= Neovascularisation extending beyond the pupil margin into the central cornea

Corneal opacification:

1=Partial obscuration of iris details

2= Iris details poorly seen with pupil margin just visible

3= Complete obscuration of iris and pupil details

Corneal keratinisation:

1=Keratinisation involving < ¼ of the corneal surface

2= Keratinisation involving > ¼ to ½ of the corneal surface

3= Keratinisation involving > ½ of the corneal surface

Table 2

Conjunctival complications:

Conjunctival hyperaemia:

1=Mild or sectoral engorgement of the conjunctival vessels

2= Moderate or diffuse engorgement of the conjunctival vessels

3= Severe hyperaemia or significant engorgement of the conjunctival vessels

Symblepharon formation:

1= Symblepharon formation only involving the conjunctival surface

2= Symblepharon formation involving < ½ of the corneal surface

3= Symblepharon formation involving > ½ of the corneal surface

Eyelid complications:

Trichiasis: (total area of the upper and lower eyelids combined)

1= Trichiasis involving less than ¼ of the lid margin

2= Trichiasis involving more than ¼ and less than ½ of the lid margin

3= Trichiasis involving more than ½ of the lid margin

Mucocutaneous junction involvement:

1=Mild irregularity of the mucocutaneous junction

2=Moderate irregularity of the mucocutaneous junction

3=Severe irregularity of the mucocutaneous junction

Meibomian gland involvement:

1= Yellowish-white oily fluid expressed

2= Thick cheesy material expressed

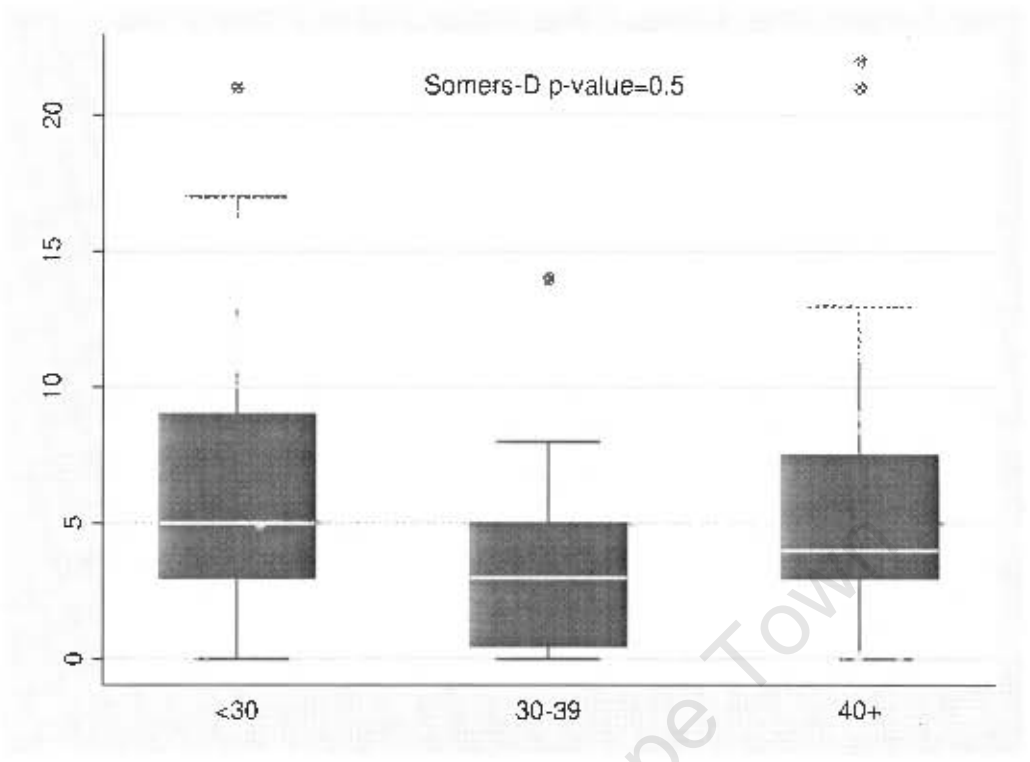
3= Inability to express any fluid

Punctal involvement:

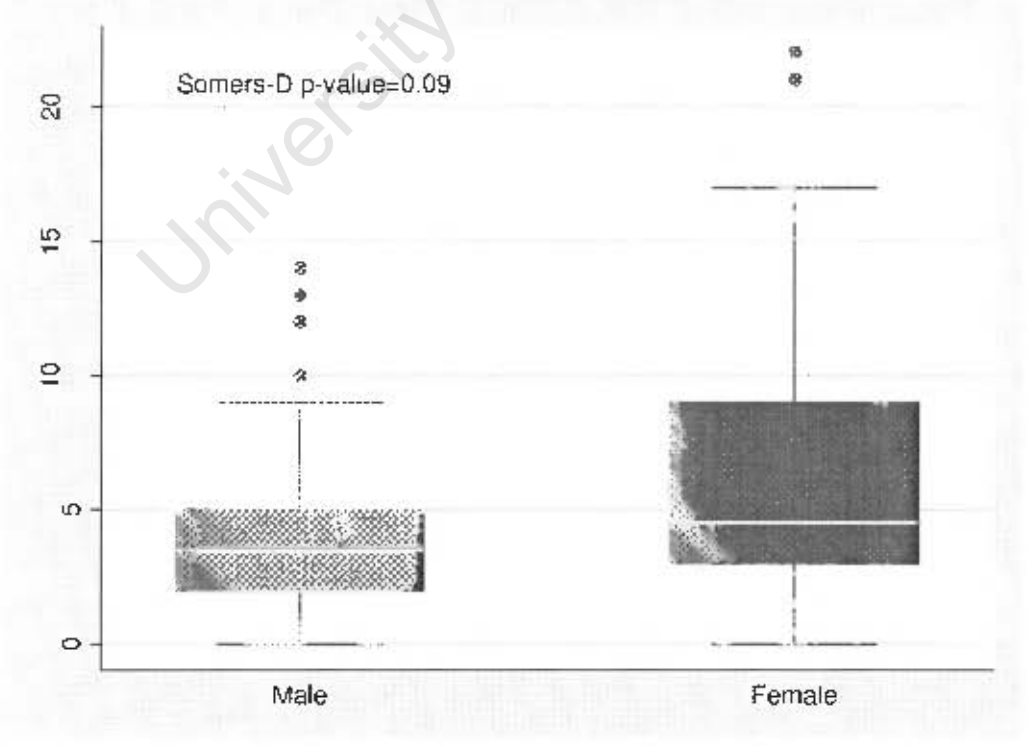
1=Iatrogenic punctual occlusion (e.g. punctal plugs or sutures)

2=either superior or inferior puncta occluded by scarring

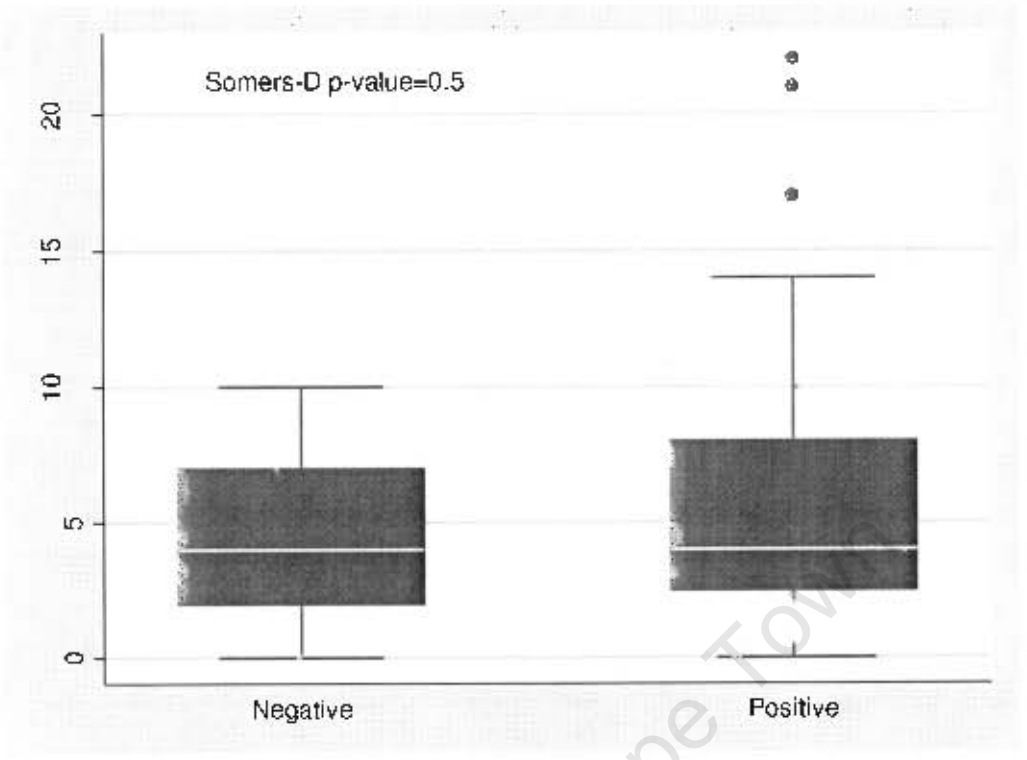
3= both superior and inferior puncta occluded by scarring



Graph 1: Box plot of severity scores by age catogories



Graph 2: Box plot of severity scores by sex



Graph 3: Box plot of severity scores by HIV status

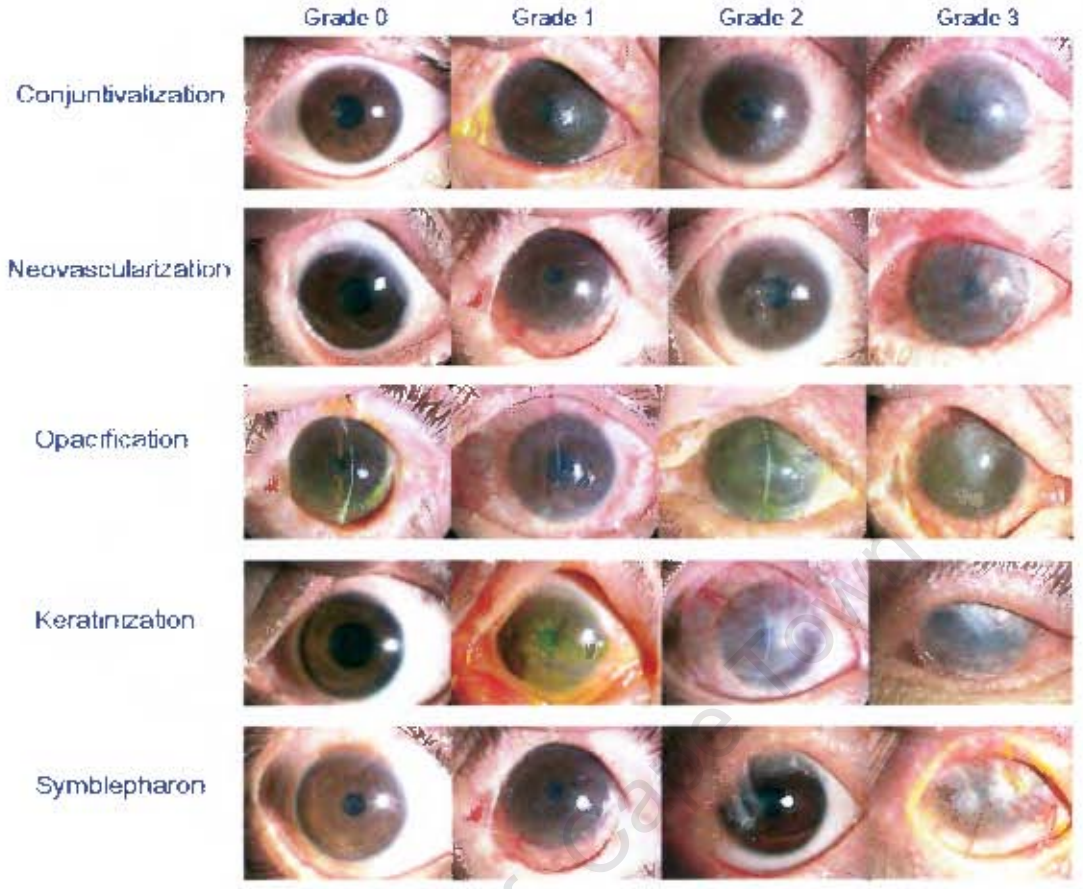


Table 3. Examples of ocular findings and their grading(Courtesy C. Sotozono)

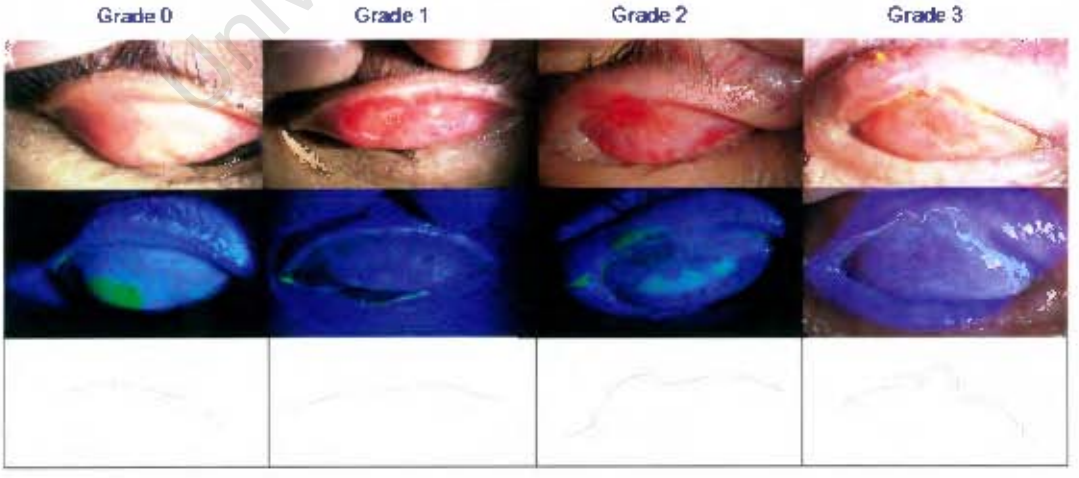


Table 4. Grading of Mucocutaneous junction involvement (Courtesy C. Sotozono)

Chapter 4

Supporting documents

- 1. Informed consent form
- 2. Patient information sheet
- 3. Guide to complications

Supporting documents

1. Informed consent form

Informed Consent Form

Stevens-Johnson syndrome and Toxic Epidermal Necrolysis Study

Prospective Research Subject: Read this consent form carefully. Ask as many questions as you like before you decide whether you want to participate in this research study. You are free to ask questions at any time before, during, or after your participation in this research.

Project Title: Prevalence of chronic complications in Stevens-Johnson syndrome and Toxic Epidermal Necrolysis.
Principal Researcher: Dr. L.M. van Zyl
Telephone: 082 875 8630
E-mail: lourensvz4@gmail.com
Organization: University of Cape Town
Location of Study: Groote Schuur Hospital, Ward D4 and Out Patients Department

Purpose of This Research Study

You are being asked to participate in a research study designed to look at what the long term effects are on the visible structures of your eyes. These structures include the skin around your eyes, your eyelids, the fleas around your eyeball called the conjunctiva and the clear part of your eye called the cornea.

The doctor in charge of this study is Dr. Lourens van Zyl who is a doctor studying to become a specialist eye-doctor. This study will be conducted as part of his degree program in a masters degree in medicine at the University of Cape Town.

Procedures

You will:

1 attend an examination session on a specific date where the research assistant will test the vision in both your eyes.
2 be examined by the research doctor with various equipment used by eye doctors like an examination microscope called a slit lamp. The doctor will put medical drops in your eyes that numb any feeling in that eye. None of the examinations will cause you any pain. There might be a slight discomfort if you are sensitive to bright light as the equipment uses electric light to help the doctor to examine you better. The examination will not take longer than 20 minutes. If the doctor feels that you need further treatment he will write you a referral letter to an appropriate hospital or clinic.

Possible Risks

There are no risks involved in participating in this study.

Possible Benefits

There is a possibility that if you are affected by the disease that we may discover that you might benefit from further treatment to give relief from the involvement of your eyes.

We as doctors might get a better understanding from your disease so that we can treat patients more successfully in future.

Financial Considerations

You will receive financial compensation for your participation to cover all your travel costs. If you have an escort due to your inability to travel alone, the escort will also be compensated. Only a sum total of one escort will be compensated and any other companions must incur their own costs. To participate in this study it will not cost you as a participant any money.

Confidentiality

Your identity in this study will be treated as confidential. Results of the study, including all collected data, may be published in the research doctor's dissertation and in possible future journal articles and professional presentations, but your name or any identifiable references to you will not be included. Your hospital number is the only identifiable reference that will be used in this study. However, any records or data obtained as a result of your participation in this study may be inspected by the persons conducting this study and/or the University's Review Board, provided that such inspectors are legally obligated to protect any identifiable information from public disclosure, except where disclosure is otherwise required by law or a court of competent jurisdiction. These records will be kept private in so far as permitted by law.

Termination of Study

You are free to choose whether to participate in this study. You may also choose to withdraw from the study or to decline to answer any questions at any time. You will not be penalized or lose any benefits to which you are otherwise entitled if you choose not to participate or choose to withdraw. You will be provided with any significant new findings developed during the course of this study that may relate to or influence your willingness to continue participation. In the event you decide to discontinue your participation in the study, please notify Dr. L.M. van Zyl (082 875 8630, 021 404 3526) of your

decision so that your participation can be terminated in an orderly fashion. All data collected on, about, or by you will be destroyed and not used in the data analysis or writing of the findings if you choose to withdraw.

Resources

Any questions you may have about this study will be answered by Dr. L.M. van Zyl (082 875 8630, 021 404 3526, e-mail: lourensvanzyl@hotmail.com) or

Dr. Karin Lecuona (079 8601377, 021 404 3526, e-mail: karin.lecuona@uct.ac.za).

Any questions you may have about your rights as a research subject will be answered by the University of Cape Town Research council, 021 406 0009

Subject and Researcher Authorization

I have read and understand this consent form, and I volunteer to participate in this research study. I understand that I will receive a copy of this form. I voluntarily choose to participate, but I understand that my consent does not take away any legal rights in the case of negligence or other legal fault of anyone who is involved in this study. I further understand that nothing in this consent form is intended to replace any applicable provincial, state, or university laws.

In case of a minor: I have read and understand this consent form, and I voluntarily consent to my child's participation in this research study. I understand that my consent does not take away any legal rights in the case of negligence or other legal fault of anyone who is involved in this study. I further understand that nothing in this consent form is intended to replace any applicable provincial, state, or university laws.

Signatures

Participant Name (printed): _____

Participant Signature: _____

Date: _____

Legal Guardian Name (printed): _____

Legal Guardian Signature: _____

Date: _____

Principal Researcher's Name (printed): _____

Principal Researcher's Signature: _____

Date: _____

Person obtaining consent, if other than principal investigator (printed):

_____

Signature: _____

Date: _____

2. Patient information sheet

Patient information sheet

Patient Sticker

Age	**Gender**			**Period after attack (months)**		
Drug	**Other eye complications** Glaucoma, Cataract, Retinopathy, Other(specify):					
Eye	**Right**			**Left**		
Visual acuity (1: 6/6-6/18, 2:6/24- 6/60, 3: <6/60)	**1**	**2**	**3**	**1**	**2**	**3**
Tonometry						
SPK	**1**	**2**	**3**	**1**	**2**	**3**
Corneal epithelial defect	**1**	**2**	**3**	**1**	**2**	**3**
Loss of POV	**1**	**2**	**3**	**1**	**2**	**3**
Conjunctivalisation	**1**	**2**	**3**	**1**	**2**	**3**
Corneal neovasc'tion	**1**	**2**	**3**	**1**	**2**	**3**
Corneal opacification	**1**	**2**	**3**	**1**	**2**	**3**

Corneal keratinisation	**1**	**2**	**3**	**1**	**2**	**3**
Conjunctival hyperaemia	**1**	**2**	**3**	**1**	**2**	**3**
Symblepharon formation	**1**	**2**	**3**	**1**	**2**	**3**
Trichiasis	**1**	**2**	**3**	**1**	**2**	**3**
Mucocutaneous junction involvement	**1**	**2**	**3**	**1**	**2**	**3**
Meibomian gland involvement	**1**	**2**	**3**	**1**	**2**	**3**
Punctal involvement	**1**	**2**	**3**	**1**	**2**	**3**

3. Guide to complications

Guide to the classification of complications

Corneal complications:

Severity of superficial punctuate keratopathy:

0: No punctuate staining
1: Staining of < $^1/_3$ of corneal surface
2: Staining of > $^1/_3$ but < $^2/_3$ of corneal surface
3: Staining of > $^2/_3$ of corneal surface

Corneal epithelial defect:

0: No epithelial defect
1: Epithelial defect involving < ¼ of the corneal surface
2: Epithelial defect involving > ¼ but < ½ of the corneal surface
3: Epithelial defect involving > ½ of the corneal surface

Loss of the palisades of Vogt (POV):

0: Presence of the entire POV
1: Loss of < ½ of the circumference of the POV
2: Loss of > ½ of the circumference of the POV
3: Total loss of the circumference of the POV

Conjunctivalisation:

0: Absence of conjunctivalisation
1: Conjunctivalisation involving < ¼ of the corneal surface
2: Conjunctivalisation involving > ¼ but < ½ of the corneal surface
3: Conjunctivalisation involving > ½ of the corneal surface

Corneal neovascularisation:

0: No neovascularisation
1: Neovascularisation confined to the corneal periphery
2: Neovascularisation extending up to the pupil margin
3: Neovascularisation extending beyond the pupil margin into the central cornea

In eyes with significant opacification and symblepharon with difficulty in evaluating corneal neovascularisation a score of 3 will be assigned

Corneal opacification:

0: Clear cornea with iris details clearly visible
1: Partial obscuration of iris details
2: Iris details poorly seen with pupil margin just visible
3: Complete obscuration of iris and pupil details

Corneal keratinisation:

0: No keratinisation
1: Keratinisation involving < ¼ of the corneal surface
2: Keratinisation involving > ¼ to ½ of the corneal surface
3: Keratinisation involving > ½ of the corneal surface

Conjunctival complications:

Conjunctival hyperaemia:

0: Absence of hyperaemia
1: Mild or sectoral engorgement of the conjunctival vessels
2: Moderate or diffuse engorgement of the conjunctival vessels
3: Severe hyperaemia or significant engorgement of the conjunctival vessels

Symblepharon formation:

0: No symblepharon
1: Symblepharon formation only involving the conjunctival surface
2: Symblepharon formation involving < ½ of the corneal surface
3: Symblepharon formation involving > ½ of the corneal surface

Eyelid complications:

Trichiasis: (total area of the upper and lower eyelids combined)

0: No trichiasis
1: Trichiasis involving < ¼ of the lid margin
2: Trichiasis involving > ¼ and < ½ of the lid margin
3: Trichiasis involving > ½ of the lid margin

Mucocutaneous junction involvement:

0: Normal mucocutaneous junction
1: Mild irregularity of the mucocutaneous junction
2: Moderate irregularity of the mucocutaneous junction
3: Severe irregularity of the mucocutaneous junction

In eyes with significant keratinisation of the lid margin or extensive symblepharon where evaluation of the lid margin is difficult, a score of 3 will be given

Meibomian gland involvement:

The severity of meibomian gland involvement is determined clinically by the nature of the gland excretion expressed manually at the centre of the upper lid

0: Clear oily fluid expressed
1: Yellowish-white oily fluid expressed
2: Thick cheesy material expressed
3: Inability to express any fluid

Punctal involvement:

0: Normal patent puncta
1: Iatrogenic punctal occlusion (e.g. punctual plugs or sutures)
2: Either superior or inferior puncta occluded by scarring
3: Both superior and inferior puncta occluded by scarring