THE NORTHERN HOSPITAL

SOFOSBUVIR

"Trilogy of the Desert: Mirage", oil on canvas, 1946, Salvador Dali, National Gallery of Victoria, Melbourne.

"The aura of classical antiquity evokes the desert flower, issuing from the forehead of Apollo"

Salvador Dali describing "Trilogy of the Desert: Mirage", 1946.

Today Salvador Dali is remembered as the supreme exponent of the Surrealist genre of the mid-Twentieth century. It is surprising to know therefore that in his own day he was not beloved by the Surrealists at all, even though in large degree their fame came off the back of his coattails! Dali was....well, Dali. Enigmatic, eccentric in the extreme, a shameless self-promoter and proud of the fact, religious but also fascinated by the latest scientific developments in atomic physics, lover of classic and Renaissance Art, worshipper of gold and the American dollar (and proud of those facts also), commercial,

Pop and Op Artist decades before Andy Warhol and Bridget Riley, devoted acolyte of Sigmund Freud, supreme narcissist, (proud of that again), traditionalist, Monarchist, Dali simply put, ran against the prevailing tide of every ideal and value most other Surrealists believed in. In the end the only thing Dalí believed in was himself, which of course only made him the more famous with the general public because of the controversy he incited wherever he went and whenever he opened his mouth.

So incensed was the self-proclaimed "Pope of Surrealism" Frenchman Andre Breton, he formally "expelled" Dali from their ranks; which was not a particularly unusual event in itself as Breton expelled virtually every Surrealist who expressed any degree of deviance from his own self proclaimed "manifesto of Surrealism" - which in the end was most Surrealists of any note. Dali of course couldn't care less and made an hilarious public mockery of the whole proceedings, to the unending agony of the "official" Surrealists. By the end of the 1930s Salvador Dali was one of the most famous figures in the Artistic world, famous not only for his astonishing and baffling works, but even more so for his outrageous antics and his unspeakable psycho-sexual perversions.

And so it was with great anticipation that the American public and press awaited the arrival of Salvador in New York City, when he fled from the Nazi invasion of France in 1940. American Artists were apprehensive of his arrival. At this time they were struggling to develop their own uniquely American style of modern Art, one that would challenge European "superiority". The genre that was generally adopted at this time that was most "avant-garde" al la America was Abstract Expressionism, led by exponents such as Jackson Pollock, Willem de Kooning, Arshile Gorky, Barnett Newman, Mark Rothko and others. The American Abstract Expressionists were having a difficult time being accepted, particularly when ridiculed by no less a personage than the President of the United States. President Harry S. Truman just didn't get Abstract Expressionism at all. In uncomprehending exasperation he described the emerging genre as, "...the splatter dash school of (modern) art, with its paintings which look as if the artist had merely hurled an egg!"

Outraged with their President, the American avant-garde looked to the great man Dali for support. But Salvador, who exulted in controversy, and to the amused delight of the American Public, agreed whole heartedly with President Truman. Not only was his lack of support for modern American art shocking, be made an hilarious mockery of the Abstract Expressionists in general by calling a Press conference! The Baltimore Sun reported this "Press Conference" with unrestrained mirth on 23 of February 1946. Dali had proceeded to smash eggs onto a blank canvas, then with great academic precision, meticulously compared the results with some of his own exquisitely rendered works. Dali was nothing if not a technical genius. He finally announced to a bemused press in the most delightful of Spanish accents; "I wholeheartedly with Mr. Truman agree! Always has been my ambition to catch in painting all traditions. Never have I liked abstractions, never! Against them I fight!"

In part to get back at Dali, the Abstractionists were pronouncing that Surrealism was dead. But Dali totally confounded them again by declaring that he totally agreed. His aim whilst in America, he declared, was to be the saviour of modern Art! But this was not actually Dali, being Dali this time, he did have a serious resolve. He felt that modern Art

was losing its way and that the way back would be to rediscover the lost traditions and the technical brilliance of the Italian Renaissance. In this regard he was challenging all forms modernism, not just abstraction. From this time on his works, though still incomprehensible to the public or to the Surrealists themselves, or even to Sigmund Freud, incorporated unmistakable motifs from the great Renaissance Artists, Raphael being his particular idol.

Whatever people thought of Salvador, no one, Surrealists or Abstractionists included could deny his technical brilliance or his unsurpassed genius for novelty. Igor Cassini told his millions of readers in the New York Journal - American - in December 1945: "Dali is perhaps the most talked about, prolific and commercially successful painter in the market. What he paints is strictly monstrous and nightmarish, but all his severest critics agree that Dali's drawings have a Michelangeloian strength and that his technique, if not his subjects, approaches that of Leonardo da Vinci". In the Cleveland News two years later, in November 1947 A. Reynolds Morse (a collector of Dali's work and personal friend) wrote, "Because of the remoteness of classical traditions unapproached by any other single artist of this century, Dali stands head and shoulders above the mob of moderns. I feel that Dali is one of the great spirits of our age....the Raphael of our age".

Many agreed with these sentiments. Even some of the Abstractionists and "official" Surrealists gave grudging respect to Dali's technical genius even if he refused to "toe party lines". What galled the most however, apart from his unmentionable Freudian psycho-sexual oddities, was his astonishing commercial success, at a time when most other modern Artists were living on the bread line. He was decades ahead of his time with regard to the commercialization and promotion of his own Art, and he would become tremendously wealthy. He worked with film and stage producers, but he also worked closely with industry and advertising companies. He even produced proto-motifs of Pop Art decades before Andy Warhol, (in his "Poetry of America - The Cosmic Athletes", 1943), we see - probably for the first time in modern Art - a hyper-realistically rendered coca cola bottle, though admittedly the bottom half of it is melting into the ground in typical Dalian fashion.

In the National Gallery of Victoria Melbourne, hangs one of Dali's most superb examples of his Renaissance style; "Trilogy of the Desert: Mirage", oil on canvas, 1946. It is a beautiful work and technically stunning. A distant mountain on the horizon may be seen as a distant past, perhaps the time of the Renaissance in the age of Raphael. We see the classical bust of the Apollo Belvedere (from the mid-Fourth century B.C) reaching out from the classical age, riding on beams of fragmented classical and Palladian architecture. Two beams carry the head of Apollo, while a third further back in the distance supports two broken arched ruins that give the appearance of a majestic bird soaring over the Catalonian desert that he loved so much. Waiting to greet Apollo from this classical age is a beautiful Renaissance maiden. Her translucent dress clings tightly to her body in a hot but gentle desert wind, revealing her voluptuous breasts, echoing Raphael's "La Fornarina" of 1518. Her legs are strong, slim and athletic, the right laced in gold ribbon. Her arms are outstretched in the style of Michelangelo, while her long golden hair is unmistakably Sandro Boticelli. On the distant horizon is one of Dali's most

recurring motifs, a microscopic lone figure in the desert, perhaps it is Dali himself, lost within the vast, terrifying and inhospitable landscape of his own subconscious mind.

But there is another dimension again to the Trilogy, now long lost to Twenty First century sensibilities, but one that would certainly not have been lost to the sensibilities of Dali's contemporaries. The maiden reaches out to a desert flower attached to Apollo's forehead. This image was homage to Dali's patron, the Shulton cosmetics company, and the American dollar. Anton Breton got some back of his own when he called Dali, admittedly quite cleverly, "Avida Dollars" - i.e he "has the dollars". Avida Dollars, in anagram is Salvador Dali. Salvador may be the saviour of modern Art, Breton was saying, but if he was, it was only by dint of the almighty dollar, rather than any restoration of the ideals of the Renaissance. Although a little unfair the criticism was not without some justification. In 1946 the Shulton Cosmetics company, (creator of "Old Spice" for men in 1937) had developed a new perfume for women they called "Desert Flower". The company promoted their new product as a "light, subtle and airy fragrance", presented in an elegant fluted glass bottle, complete with white and gold packaging. As Dali promoted his return to the Renaissance, the Shulton Cosmetics company their saw a chance to cash in with their own return to classical elegance for the women of America. Salvador Dali remained true to his dream of saving modern Art by restoring the old ideals, but at the same time he also recognized modern financial imperatives. Many were cynical of his motives, but he had the last laugh in the end becoming a wealthy man

Sofosbuvir is one of the latest miracle anti-viral agents used in the treatment of hepatitis C. In years past this diagnosis could be a life sentence, and in many of these cases ultimately a death sentence. But today a compete cure, previously unimaginable, is now possible in over 90% of cases. And so why does not medical science apply the same determination of purpose to every human disease? It is not for a lack of enthusiasm on the part of the Medical profession, but rather a lack of funding from Big Pharma business. The cost of targeted drug research and development in the modern age is of galactic proportions, in some cases amounting to billions of dollars being spent from the research stage to formulations sitting on our Pharmacy shelves. The DAA anti-hepatitis C drugs are one such example par excellence. The stakes for big business are high indeed. Failure can mean financial ruin, while success may ensure the riches of Aladdin's cave itself. It is for this reason that only certain medical conditions will be attractive prospects for modern targeted drug development. Where disease incidence is high, the rewards of a successful development of novel drug will be high. However for diseases with relatively low incidence, no matter how devastating or deadly, the financial incentive and reward may be virtually non-existent. Brilliant scientists who, true to their ideals, strive to find cures for diseases must sometimes, like the maestro Salvador Dali, come to terms with the pragmatic realities of their own modern Arts.

SOFOSBUVIR

Introduction

Sofosbuvir (trade name "Sovaldi") is a **pan-genotypic** inhibitor of the specific **Hepatitis C Virus NS5B - RNA-dependent RNA polymerase**, which is *essential* for **Hepatitis C Virus** replication.

Sofosbuvir is used in **combination** with **other anti-hepatitis C drugs** in order to reduce the chances for the development of **viral resistance**.

The best combination of drugs will be directed by the exact Hepatitis C genotype that is being treated, as well as the stage of disease and consideration of other comorbidities, however in general terms the combination of **sofosbuvir** and **velpatasvir** is currently effective against all hepatitis C genotypes.

Over 90% of patients have a sustained response to 12 weeks of treatment with sofosbuvir and velpatasvir. This is irrespective of their hepatitis C genotype, cirrhosis status or previous experience with treatment.

History

Sofosbuvir is one of a group of **direct acting anti-hepatitis C virus** agents.

These agents replaced older treatments involving interferon and ribavirin, which required much longer treatment periods, had significantly more adverse effects and were only around 70% effective.

The first **direct acting anti-hepatitis C virus** agents were introduced into clinical practice in 2011

Sofosbuvir was developed in 2007 and introduced into clinical practice in the US in 2013.

Chemistry

Sofosbuvir (a prodrug)

↓ *Metabolized (via three phosphorylation steps)*

Uridine analog triphosphate (GS-461203) (active agent)

↓ *Dephosphorylation (via an irreversible step)*

Nucleoside metabolite GS-331007 (non-active)

Classification

Currently available **anti-hepatitis C drugs** - called **Direct Acting Antivirals** (or **DAAs**) (or more specifically - Direct acting anti-hepatitis C virus drugs) target specific non-structural proteins that are essential for the replication of the hepatitis C virus.

3 groups are currently available:

1. Non-structural protein 3/4A (**NS3/4A**) protease inhibitors:

   Examples include:

   - Simeprevir
   - Paritaprevir
   - Asunaprevir

2. Non-structural protein 5B (**NS5B)** RNA-dependent RNA polymerase inhibitors:

   - Nucleotide polymerase inhibitors:

     Nucleoside (or nucleotide) inhibitors are analogues of the naturally occurring polymerase substrates and cause premature chain termination when incorporated into the developing nucleic acid chain.

     Since the HCV NS5B polymerase's active site is highly conserved across genotypes, (or nucleotide) inhibitors tend to have similar antiviral activity across all HCV genotypes, referred to as pan-genotypic activity

     Examples include:

     ♥ **Sofosbuvir**

   - Non-nucleotide polymerase inhibitors:

     The non-nucleoside polymerase inhibitors bind distal to the catalytic site, are less likely to have pan-genotypic activity, and have thus far demonstrated a lower genetic barrier to resistance.

     Examples include:

     ♥ Dasabuvir

     ♥ Daclatasvir

3. Non-structural protein 5A (**NS5A)** inhibitors:

Examples include:

- Velpatasvir
- Ledipasvir
- Ombitasvir

Preparations

Sofosbuvir as:

Tablets:

- 400 mg.

Tablets: Fixed-dose combination with ledipasvir:

- Sofosbuvir 400 mg + ledipasvir 90 mg

Tablets: Fixed-dose combination with velpatasvir:

- Sofosbuvir 400 mg + velpatasvir 100 mg

Mechanism of Action

There are at least 6 major genotypes of HCV, termed 1, 2, 3 4, 5, and 6.

Each of these genotypes can be further subdivided (e.g. 1a, 1b etc.)

At present the main genotypes found in the Australian population are:

- Genotype 1 (54%)
- Genotype 3 (37%)

Currently available **anti-hepatitis C drugs** - called **D**irect **A**cting **A**ntivirals (or **DAAs**) (or more specifically - Direct acting anti-hepatitis C virus drugs) target specific non-structural proteins that are essential for the replication of the hepatitis C virus, (**see also Appendix 1 below**).

Sofosbuvir is a **pan-genotypic** (i.e acts on all 6 genotypes) inhibitor of the specific **Hepatitis C Virus NS5B - RNA-dependent RNA polymerase**, which is *essential* for **Hepatitis C Virus** replication.

It is a pyrimidine nucleotide analog of NS5B.

Sofosbuvir is a nucleotide **prodrug** that undergoes **intracellular metabolism** to form the *pharmacologically active* **uridine analog triphosphate** (GS-461203), which is then incorporated by the HCV NS5B RNA polymerase enzyme that then acts as a **chain terminator** - thus **blocking viral replication**.

Pharmacodynamics

Sofosbuvir is a **pan-genotypic** (i.e acts on all 6 genotypes) inhibitor of the specific **Hepatitis C Virus NS5B - RNA-dependent RNA polymerase**

Over 90% of have a sustained response to 12 weeks of treatment with sofosbuvir and velpatasvir. This is irrespective of their hepatitis C genotype, cirrhosis status or previous experience with treatment.

Note that, as for all antivirals, the prevalence of viral resistance may vary geographically and over time for selected species and local information on resistance is also important, particularly when treating severe infections.

Pharmacokinetics

Absorption:

- Sofosbuvir is administered orally.

  Note that Sofosbuvir is a substrate of the **drug cell membrane transporters P-gp** and **BCRP,** while (GS-331007 is not).

  As such, sofosbuvir should not be administered with potent inducers of intestinal P-gp, such as rifampin and Saint John's Wort, which may result in reduced absorption.

Distribution

- Sofosbuvir is approximately 61-65% bound to human plasma proteins
- It is unknown if sofosbuvir crosses the human placenta.
- It is unknown if sofosbuvir is distributed into human breast milk.

Metabolism and excretion:

- Sofosbuvir is extensively metabolized in the liver to form the **pharmacologically active** uridine analog triphosphate (GS-461203).

  Sofosbuvir has a relatively short half-life of just 0.5 0.8 hours.

  The active metabolite, (**GS-461203)** has a **long half-life** of approximately 18 hours, so is supportive of once daily dosing.

- GS-461203 is irreversibly metabolized to the **inactive phosphate free metabolite** of the nucleotide, known as GS-331007.

Indications

Sofosbuvir is used **in combination** with **other anti-hepatitis C drugs** in order to **reduce the chances** for the development of **viral resistance**.

Monotherapy of **sofosbuvir** is **not** recommended.

In general terms **sofosbuvir** is currently indicated for chronic **hepatitis C**, *with* **other anti-hepatitis C antivirals.**

For fixed-dose combination **sofosbuvir** with **velpatasvir**:

- Chronic hepatitis C (**all genotypes**)

For fixed-dose combination with ledipasvir:

- Chronic hepatitis C (genotype 1, 4, 5 or 6 infection)

For fixed-dose combination with velpatasvir and voxilaprevir

- Chronic hepatitis C, after treatment failure with either:
  - ♥ An NS5A inhibitor regimen (any genotype)
  - ♥ Sofosbuvir without an NS5A inhibitor regimen (genotype 1a or 3)

Contra-indications/precautions

Sofosbuvir has not been studied **alone** and so the relative contributions to various side effects are uncertain.

In general terms however **sofosbuvir** appears to be well tolerated.

The most common adverse effects seen in trials with **sofosbuvir** and ribavirin were:

1. Insomnia
2. Fatigue
3. Headache
4. Pruritis
5. Anaemia.

For fixed-dose combination with **ledipasvir**::

1. Nausea and diarrhoea are common

2. Angioedema (rarely)

For fixed-dose combinations with **velpatasvir** or **voxilaprevir**:

1. Nausea is common.

Pregnancy

Sofosbuvir is currently classified as a category B1 drug with respect to pregnancy.

Category B1 drug are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

It is not known however if sofosbuvir/velpatasvir is safe for pregnant women as there have been no adequate studies.

Breast feeding

It is not known if sofosbuvir/velpatasvir is safe for breast feeding women as there have been no adequate studies.

Adverse Effects

1. Hepatitis B virus reactivation:

    - Antivirals used for chronic hepatitis C may *reactivate* **hepatitis B virus**; screen for current or previous hepatitis B infection before starting treatment.

2. Drug interactions:

    Important interactions include:

    - With amiodarone, the risk of bradycardia (potentially fatal) may be increased by treatment with sofosbuvir (when given with anti-HCV antivirals other than ribavirin).

    - Fixed-dose combination with velpatasvir and voxilaprevir: treatment with **rifampicin** or **rosuvastatin** is contraindicated.

3. Renal impairment:

- Sofosbuvir concentration increases in renal impairment.

  There is limited data for use when the eGFR is < 3 0 mL/minute/1.73 m^2; other agents are preferred, seek specialist advice.

4. Hepatic impairment:

- Fixed-dose combination with velpatasvir and voxilaprevir: not recommended in moderate-to-severe hepatic impairment (Child-Pugh class B or C) as voxilaprevir concentrations increase significantly.

Dosing

Treatment regimes must be individualized for each patient.

However, it *general* terms, the following is currently used: [2]

Usual adult (> 18 years) dosing for **Sofosbuvir** is:

- 400 mg once daily.

Current combination regimes include:

For fixed-dose combination **sofosbuvir** with **velpatasvir**:

- 1 tablet once daily for 12 weeks.

  For decompensated cirrhosis or genotype 3 with compensated cirrhosis, ribavirin may be added, see Dosage in Ribavirin.

For Sofosbuvir with **ribavirin**:

- Genotype 2 or 3 *or* awaiting liver transplant, treat:

  For 12 weeks in genotype 2 infection

  For 16 weeks in genotype 3 infection (24‑week treatment may be necessary)

  Until liver transplant.

For **Sofosbuvir** with **daclatasvir**:

- Genotype 1 or 3:

  Treat for 12 weeks (24 week treatment may be necessary).

Ribavirin may be added for patients with cirrhosis, see Dosage in Ribavirin.

For fixed-dose combination **Sofosbuvir** with ledipasvir:

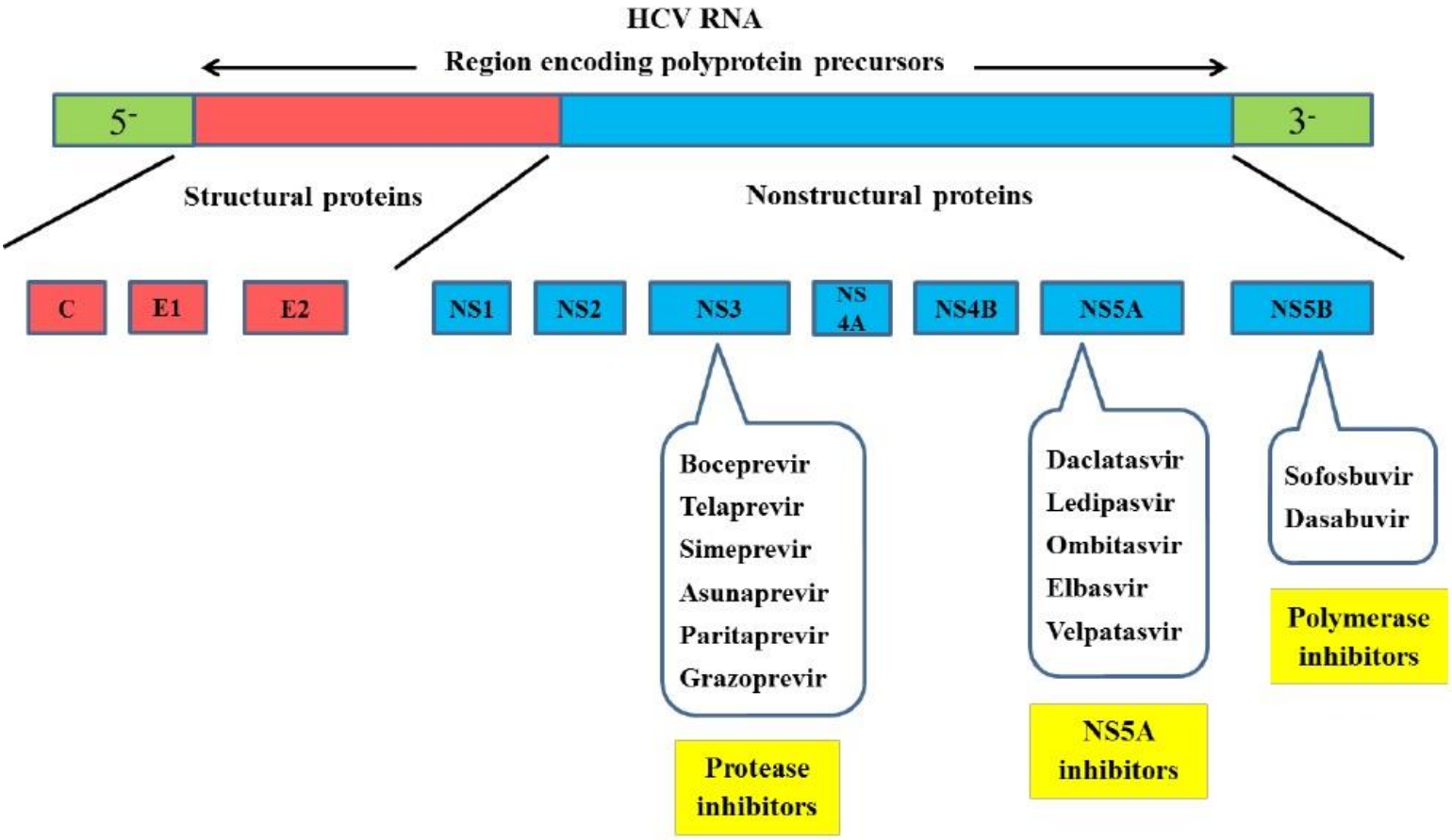
- 1 tablet once daily for 8 or 12 weeks (24 week treatment may be necessary).

  Ribavirin may be added, see product information for circumstances and Dosage in Ribavirin.

For fixed-dose combination with **velpatasvir** and **voxilaprevir**:

- 1 tablet once daily for 12 weeks.

Appendix 1



Proteins encoded by the hepatitis C virus genome as targets for the direct acting antiviral agents used in the treatment of chronic hepatitis C infection. (Ayman Geddawy et al, 2017).

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3. Sofosbuvir in MIMs Website, 1 August 2019.

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Further reading:

Dr Ted Gott on "Trilogy of the Desert", Triennial Special Issue vol 2 NGV, June 2018.

Dr J. Hayes
1 November 2019.