THE PRESCRIRE AWARDS FOR 2021

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2021 Prescrire Drug Awards

Every month, in the Marketing Authorisations section, Prescrire's Editorial Staff points out which of the multitude of newly authorised products or indications are worth adding to the list of useful treatment options, and which are to be avoided. These conclusions are based on systematic analyses of the relevant evaluation data available on new drugs, new indications for drugs already authorised in a different clinical situation, and new pharmaceutical forms or new dose strengths of existing drugs.

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The 2021 Prescrire Drug Awards are based on the analyses published in the Marketing Authorisations section of our French edition in 2021. These awards recognise products that represent a therapeutic advance, in that they offer better efficacy than existing treatments, provoke less frequent or less severe adverse effects (provided they also have similar efficacy), or enable a useful drug to be used more safely or easily.

Nine drug awards in 2021, including two Pilules d'Or

Two drugs examined in 2021 represent a major therapeutic advance worthy of a Pilule d'Or (Golden Pill Award). Five drugs earned a place on the 2021 Honours List, and two drugs made the Noteworthy list.

Tozinameran, elasomeran and covid-19: marked reduction in the risk of developing symptomatic disease, including severe disease. One of the key developments of 2021 was the advent of several covid-19 vaccines. Two of them are based on messenger ribonucleic acid (mRNA): *tozinameran* (Comirnaty®, BioNTech and Pfizer) and *elasomeran* (Spikevax®, Moderna).

In trials conducted in 2020 during the pandemic in tens of thousands of people, these two vaccines greatly reduced the risk of developing symptomatic covid-19 in the short term. Numerous epidemiological studies conducted in 2020 and 2021 showed these vaccines to be effective at preventing severe forms of covid-19 during the months following vaccination, including covid-19 caused by most of the Sars-CoV-2 variants circulating in 2021. One major unknown is how effective they will be against any new variants that emerge.

These vaccines' efficacy in adolescents is probably similar to that in adults. But as covid-19 is rarely serious in adolescence, vaccination is of more limited personal benefit in this age group. Mass vaccination probably benefits everyone, by reducing the societal effects of the epidemic.

As with other vaccines, the main short-term adverse effects of *tozinameran* and *elasomeran* are frequent local and systemic reactions. Very rare cases of pericarditis and myocarditis were reported during the vaccination campaigns, especially in adolescents and young men. Most cases resolved within a few days. The other serious adverse effects reported after receiving one of these vaccines were mainly hypersensitivity reactions, Guillain-Barré syndrome, acquired haemophilia and viral reactivation. Unknowns remain over their possible long-term adverse effects.

These two vaccines represented a major therapeutic advance in the context of the covid-19 pandemic in 2021, and both have therefore been awarded a Pilule d'Or. They constitute an additional means of prevention, alongside measures aimed at reducing transmission, such as physical distancing, hand and respiratory hygiene, and the use of face masks.

Nasal glucagon: easier to use than subcutaneous or intramuscular forms. *Glucagon*, a hormone that raises blood glucose levels, is an essential drug for treating hypoglycaemia in patients with insulin-treated diabetes who have lost consciousness.

Glucagon has been available for many years as a powder for reconstitution as a solution for subcutaneous or intramuscular injection.

Glucagon is now marketed in Europe as a powder for administration as a dry nasal spray (Baqsimi®). Intranasally administered and injected *glucagon* have similar efficacy. The ease of use of the ready-to-use spray device is a therapeutic advance in a situation where urgent treatment is required, especially in non-medical settings, earning nasal glucagon a place on this year's Honours List. It is important that the carers, family and friends of patients with diabetes know when and how to use this product.

Covid-19 vaccines Ad26.CoV2-S and ChAdOx1-S: when mRNA vaccines are not available. In addition to the mRNA covid-19 vaccines, two viral vector covid-19 vaccines were authorised in the European Union in 2021: *covid-19 vaccine Ad26.CoV2-S* (Covid-19 Vaccine Janssen®, Janssen-Cilag) and *covid-19 vaccine ChAdOx1-S* (Vaxzevria®, AstraZeneca).

In trials conducted in tens of thousands of people in 2020 during the pandemic, these two vaccines reduced the risk, in the short term, of developing symptomatic covid-19 and of hospitalisation for covid-19. One major unknown is how effective they will be against any new Sars-CoV-2 variants that emerge.

The short-term adverse effects of these two vaccines are those common to most vaccines, mainly frequent local and systemic reactions. Rare but serious thromboses, with thrombocytopenia or haemorrhage, were identified as adverse effects during the vaccination campaigns. As with the mRNA covid-19 vaccines, unknowns persist over their long-term adverse effects.

In practice, these thromboses are sufficiently serious to position these two vaccines, as of 2021, as second-tier options after mRNA covid-19 vaccines. They were particularly useful in

2021 Prescrire Drugs Awards

2021 Pilule d'Or / Golden Pill

A Pilule d'Or (Golden Pill) is granted to drugs that represent a major therapeutic advance in a field in which no treatment was previously available.

- **COMIRNATY® (*tozinameran*) – BioNTech (representative in France: Pfizer)**
- **SPIKEVAX® (*elasomeran*) – Moderna**

For active immunisation against the virus Sars-CoV-2 to prevent covid-19 disease (*Prescrire Int* n° 227, 231, 236).

2021 Honours List

Drugs included on the Honours List constitute a clear advance for some patients compared with existing therapeutic options, albeit with limitations.

- **BAQSIMI® (*nasal glucagon*) – Lilly**
  In severe hypoglycaemia in diabetic patients aged 4 years and over (*Prescrire Int* n° 232).
- **COVID-19 VACCINE JANSSEN® (*covid-19 vaccine Ad26.CoV2-S*) – Janssen-Cilag**
  For active immunisation against the virus Sars-CoV-2 to prevent covid-19 disease (*Prescrire Int* n° 229).
- **GIVLAARI® (*givosiran*) – Alnylam**
  In acute hepatic porphyria in patients aged 12 years and over (*Prescrire Int* n° 227).
- **MABTHERA® or other brands (*rituximab*) – Roche**
  In moderate to severe pemphigus vulgaris in adults (*Prescrire Int* n° 226).
- **VAXZEVRIA® (*covid-19 vaccine ChAdOx1-S*) – AstraZeneca**
  For active immunisation against the virus Sars-CoV-2 to prevent covid-19 disease (*Prescrire Int* n° 229).

Noteworthy in 2021

Drugs deemed "Noteworthy" provide a modest improvement in patient care.

- **JORVEZA® (budesonide orodispersible tablets) – Dr. Falk Pharma**
  In eosinophilic oesophagitis in adults (*Prescrire Int* n° 234).
- **KAFTRIO® (*ivacaftor + tezacaftor + elexacaftor*) – Vertex Pharmaceuticals**
  In cystic fibrosis in patients aged 12 years and over with at least one F508del mutation in the CFTR gene (*Prescrire Int* n° 235).

2021 in geographical regions where logistics, availability or cost prevented access to mRNA covid-19 vaccines, and made their use unfeasible. These two vaccines, which constitute an additional arm in the fight against the covid-19 epidemic, therefore feature on this year's Honours List.

Givosiran in acute hepatic porphyria: fewer attacks, and no further attacks for some patients, at least in the short term. Acute hepatic porphyrias are rare conditions, characterised by the accumulation of certain toxic precursors of haem, a molecule containing ferrous iron, present for example in haemoglobin. This provokes serious attacks, marked by severe abdominal pain, often accompanied by neurological and psychiatric disorders. These attacks constitute a medical emergency, and are sometimes fatal if untreated. The long-term complications are renal, hepatic and neurological.

Haem arginate is the standard treatment for attacks, and it is sometimes used off-label to prevent attacks. Preventive treatment with *haem argenate* is burdensome, requiring one to four intravenous infusions per month.

Givosiran (Givlaari®) is a "small interfering" ribonucleic acid (siRNA), which has been authorised in the prevention of acute hepatic porphyria attacks. In a double-blind, randomised, placebo-controlled trial in 94 patients, the estimated rate of attacks requiring hospitalisation, an urgent medical consultation or administration of *haem arginate* was 3 attacks per patient per year in the *givosiran* group, versus 12 attacks per patient per year in the placebo group. 50% of the patients in the *givosiran* group had no attacks during this 6-month trial, versus 17% in the placebo group.

Givosiran's main adverse effects are injection site reactions, hypersensitivity reactions, hepatic disorders and renal disorders, including renal failure. *Givosiran* is a more convenient preventive treatment than *haem arginate*, because it is administered once a month by subcutaneous injection.

These data earned *givosiran* a place on the 2021 Honours List. The possibility that *givosiran* prevents the long-term complications of the disease is a hypothesis that remains unproven as of late 2021.

Rituximab in moderate to severe pemphigus vulgaris: more patients achieve sustained remission. Pemphigus vulgaris is a rare, potentially serious, and sometimes fatal, chronic autoimmune disease characterised by blistering and erosions on the skin and mucous membranes.

Rituximab (Mabthera° or other brands) was evaluated in this clinical situation in two comparative trials: in one trial, it was added to systemic corticosteroid therapy and compared with corticosteroid therapy alone; and in the other trial, it was compared with *mycophenolate mofetil*, an immunosuppressant sometimes used in this situation, in patients who were all receiving an oral corticosteroid. *Rituximab* increased the chances of achieving remission in both trials. In the trial of *rituximab* added to corticosteroid versus corticosteroid alone, the median duration of remission was 16 months in the *rituximab* group, versus 4 months in the other group. In the other trial, after one year of treatment, 40% of patients in the *rituximab* group had been in complete remission for at least 16 consecutive weeks, versus 9.5% in the *mycophenolate mofetil* group.

Rituximab's main adverse effects are infections, infusion reactions, hypersensitivity reactions, cardiac disorders, haematological disorders, interstitial lung disease and cancer.

Rituximab was awarded a place on the 2021 Honours List for its demonstrated efficacy in pemphigus vulgaris.

Budesonide orodispersible tablets in eosinophilic oesophagitis: symptom relief in about half of patients. Eosinophilic oesophagitis is a chronic immune-mediated disease. Its symptoms, such as dysphagia, cause feeding difficulties that can greatly affect the patient's daily life. Potential complications are: complete blockage of the oesophagus with food, requiring endoscopy to clear the obstruction; more rarely, oesophageal rupture or perforation; and in the longer term, fibrosis of the oesophagus.

In two trials in just over 200 patients, about an additional 50% of patients in the groups treated with *budesonide* orodispersible tablets (Jorveza°) obtained relief from the symptoms of dysphagia as compared with the placebo groups.

The main adverse effects of *budesonide* orodispersible tablets are local candidiasis and the systemic adverse effects of corticosteroids, especially with prolonged use. The availability of orodispersible tablets, backed up by the assurances that marketing authorisation provides, is a welcome development in this situation, in which forms of *budesonide* intended for inhalation were sometimes used off-label.

The therapeutic advance provided by these orodispersible tablets warrants a place amongst this year's Noteworthy drugs. It is a shame, however, that continuous treatment was not compared with an intermittent treatment strategy in which *budesonide* would only be taken if symptoms recur, thus reducing the likelihood of experiencing the drug's adverse effects.

Ivacaftor + tezacaftor + elexacaftor in cystic fibrosis with at least one F508del mutation: alleviation of respiratory symptoms, and sometimes fewer exacerbations. Cystic fibrosis is a serious genetic disorder caused by mutations in the gene encoding the CFTR (cystic fibrosis transmembrane conductance regulator) protein. The most common mutation is the F508del (or deltaF508) mutation.

In patients with cystic fibrosis and at least one F508del mutation in the CFTR gene, triple therapy with the CFTR "modulators" *ivacaftor* + *tezacaftor* + *elexacaftor* (Kaftrio°) alleviated respiratory symptoms in four comparative trials, with a maximum duration of 24 weeks, in a total of 943 patients. *Ivacaftor* + *tezacaftor* + *elexacaftor* also reduced the incidence of exacerbations in heterozygous patients with one F508del mutation and a second mutation that results in minimal CFTR protein function.

The efficacy of *ivacaftor* + *tezacaftor* + *elexacaftor* triple therapy must be weighed against its harms, in particular upper respiratory tract infections, liver disorders, rash, muscle disorders and numerous drug interactions.

This triple therapy was deemed noteworthy mainly because of this demonstrated efficacy, albeit largely symptomatic and short-term. Any longer-term harms or possible effect on disease progression are as yet unknown.

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