dasatinib (SPRYCEL° and other brands) in children with acute lymphoblastic leukaemia

NOTHING NEW

Bias in the comparison with *imatinib* makes the favourable results obtained for *dasatinib* impossible to intepret. More than two years after its authorisation, the oral liquid form of *dasatinib*, for children unable to swallow tablets, is still not marketed in France.

SPRYCEL° - *dasatinib* tablets and powder for oral suspension

- **20 mg**, **50 mg**, **70 mg**, **100 mg** or **140 mg** of *dasatinib* per tablet
- **10 mg** of *dasatinib* per ml of reconstituted suspension. The tablets and oral suspension are not bioequivalent.

antineoplastic; tyrosine kinase (including BCR-ABL) inhibitor

New indication: newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukaemia in combination with chemotherapy in children. [EU centralised procedure]

Acute lymphoblastic leukaemia is the most common childhood cancer and accounts for about 80% of childhood leukaemias. In about 5% of cases, the malignant cells contain an abnormal chromosome called the Philadelphia chromosome. Its presence is associated with a poor prognosis. First-line treatment in this situation is generally chemotherapy divided into several phases (induction, consolidation, maintenance) with *imatinib*, a tyrosine kinase inhibitor that includes the kinase BCR-ABL among its targets (1-3).

Dasatinib (Sprycel°, Bristol Myers Squibb) is another tyrosine kinase inhibitor that includes BCR-ABL among its targets. It has been granted marketing authorisation in the European Union as first-line therapy added to chemotherapy for children with Philadelphia chromosome-positive acute lymphoblastic leukaemia (3,4).

The application to obtain marketing authorisation for *dasatinib* in this situation was based on data from a non-comparative trial. An indirect comparison of these data with those from a cohort of historical controls who received *imatinib* added to chemotherapy did not show *dasatinib* to be an advance over *imatinib* (4). Since this evaluation, additional data have become available from a randomised, non-blinded, head-to-head trial of *dasatinib* versus *imatinib*, added to chemotherapy (see "Failure to demand solid evidence for marketing authorisation spells danger for patients" p. 13).

This comparative trial included 189 children (median age 8 years) with Philadelphia chromosome-positive acute lymphoblastic leukaemia (5). The daily dose of *imatinib* in this trial was 300 mg/m², which is less than the minimum dose of 340 mg/m² per day recommended in the European marketing authorisation. This biased the comparison in favour of *dasatinib* and weakens the quality of the evidence (3,5). After a median follow-up of about 26 months for the 161 patients still alive at the time of the analysis, the estimated 4-year overall survival was about 88% with *dasatinib* versus 69% with *imatinib* (p=0.04) (5).

The known adverse effects of *dasatinib* are similar to those of *imatinib* and include: bleeding events, gastrointestinal disorders, sodium and water retention and oedema, pleural effusion, haematological disorders, myalgia, heart failure, arrhythmias, infections (including hepatitis B reactivation), dyspnoea, interstitial lung disease, pulmonary arterial hypertension, hepatic and pancreatic disorders, and skin disorders (including Stevens-Johnson syndrome). There have also been reports of nephrotic syndrome, thrombotic microangiopathy and, in children, abnormal bone growth or development. The trial comparing *dasatinib* versus *imatinib* added no new information to this adverse effect profile (3,5,6).

For children who find it difficult to swallow tablets, *imatinib* tablets can be dispersed in water or apple juice, which is not the case with *dasatinib* tablets. If tablets of differing strengths are present in the home (due to the dose adjustment required as the child's body weight increases), it is important to warn the child's carers about the risk of dosing errors. The different packaging colours for the various dose strengths help to distinguish between doses (3).

More than 2 years have elapsed since the oral liquid form of *dasatinib* was authorised in the European Union in mid-2018, yet it has still not been marketed in France (3).

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Literature search up to 31 July 2020

In response to our request for information, Bristol Myers Squibb provided us with no documentation on its product.

1- Prescrire Editorial Staff "Imatinib and acute lymphoblastic leukaemia in children. Prolonged survival in Philadelphia chromosome-positive cases" *Prescrire Int* 2015; **24** (157): 38-39.
2- National Comprehensive Cancer Network "Pediatric acute lymphoblastic leukemia" 25 November 2019: 118 pages.
3- European Commission "SPC-Sprycel" 13 February 2020 + "SPC-Glivec" 3 April 2020: 150 pages.
4- EMA - CHMP "Public assessment report for Sprycel. EMEA/H/C/000709/II/0059" 13 December 2018: 80 pages.
5- Shuhong S et al. "Effect of dasatinib vs imatinib in the treatment of pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia. A randomized clinical trial" *JAMA Oncol* 2020; **6** (3): 358-366 + supplementary material: 53 pages.
6- Prescrire Rédaction "Dasatinib (Sprycel°) et leucémie myeloïde chronique chez certains enfants et adolescents" *Rev Prescrire* 2019; **39** (433): 816-817.

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EDITORS' OPINION

Failure to demand solid evidence for marketing authorisation spells danger for patients

In order to minimise the dangers of drugs, marketing authorisation should be granted on the basis of a rigorous evaluation, which in most cases will involve double-blind randomised trials comparing the drug against a standard treatment, showing that the drug represents a tangible therapeutic advance for patients. And at least two trials are required to ensure that the findings are reproducible (1,2).

Unfortunately, in 2020, it is clear that pharmaceutical companies generally do not respect these requirements, and the European Medicines Agency (EMA) does not insist that they do so. Consequently, most applications are based on a single clinical trial.

The application to extend *dasatinib*'s indications to include children with acute lymphoblastic leukaemia illustrates this issue: the extension of indication was approved on the basis of non-comparative data alone, without the EMA demanding more information (see "Dasatinib in children with acute lymphoblastic leukaemia" p. 12).

In certain very specific situations, non-comparative data are sometimes acceptable, for example in a condition for which an urgent, unmet medical need exists or a serious condition that is so rare that it is impossible to recruit enough patients for a comparative trial (1). The use of *dasatinib* in children with acute lymphoblastic leukaemia does not meet these criteria. A treatment of the same type with a favourable harm-benefit balance is already available for these children. Furthermore, a randomised comparative trial versus *imatinib* has now been conducted. Its results were published just a few months after *dasatinib* was granted marketing authorisation in this situation, thus proving that a comparative evaluation would have been feasible (3).

In March 2020, the EMA rightly urged the scientific community to conduct randomised comparative trials designed to generate robust evidence on covid-19 (4). It would be helpful if the EMA adopted the same attitude towards other clinical situations, to better serve patients and build confidence in its work.

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1- Prescrire Editorial Staff "Adaptive pathways: EMA's dangerous plan" *Prescrire Int* 2016; **25** (174): 223.
2- Prescrire Rédaction "Évaluer le progrès thérapeutique: avec méthode, au service des patients" *Rev Prescrire* 2015; **35** (382): 565-569.
3- Shuhong S et al. "Effect of dasatinib vs imatinib in the treatment of pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia. A randomized clinical trial" *JAMA Oncol* 2020; **6** (3): 358-366 + supplementary material: 53 pages.
4- Prescrire Editorial Staff "Evidence required: for covid-19 too" *Prescrire Int* 2020; **29** (218): 199.

risankizumab (SKYRIZI°) and plaque psoriasis

NOTHING NEW

According to several clinical trials in patients with moderate to severe plaque psoriasis, *risankizumab* (an interleukin-23 inhibitor) was more effective in reducing lesions than *adalimumab* (a TNF-alpha inhibitor), *ustekinumab* (an interleukin-12 and interleukin-23 inhibitor) and *secukinumab* (an interleukin-17A inhibitor). However, given the limited experience with use of *risankizumab*, it is preferable to initially use a TNF-alpha inhibitor. And when such a drug fails, the efficacy and adverse effect profile of *risankizumab* seem similar to those of *guselkumab* (another interleukin-23 inhibitor), even though *risankizumab*'s evaluation is more extensive. In summary, *risankizumab* does not provide a therapeutic advance for patients.

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romiplostim (NPLATE°) and chronic immune thrombocytopenia from one year of age

NOTHING NEW

Like *eltrombopag*, *romiplostim* increases platelet counts in the short term in children after standard treatments have failed, but with no demonstrated effect in reducing the number of bleeding episodes. Its adverse effect profile in children is similar to that in adults, and additionally includes oropharyngeal and abdominal pain, and rhinitis. There is a risk of error when preparing the drug for administration.

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