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Use of rifapentine in the treatment of latent tuberculosis infection

Summary

Une production de l'Institut national d'excellence en santé et en services sociaux (INESSS)

Direction du médicament

Québec

SUMMARY

Use of rifapentine in the treatment of latent tuberculosis infection

Introduction

Tuberculosis (TB), an infectious and contagious disease mainly caused by *Mycobacterium tuberculosis*, usually presents as pulmonary damage. Although curable, TB is one of the main causes of deaths attributed to infection worldwide. People who are exposed to a TB case but do not develop active TB may have latent TB infection (LTBI). Without appropriate treatment, reactivation may occur in approximately 5% to 10% of LTBI cases [WHO, 2015]. In Quebec, TB outbreaks have occurred among Inuit populations living in remote and isolated regions in Nunavik, persons in a situation of marginalisation in urban settings, prison inmates and new immigrants and refugees. Rifapentine is used in combination with isoniazid to treat LTBI in some countries, including the United States. However, rifapentine is not marketed in Canada and is only imported on an exceptional basis. Treatment options such as isoniazid and rifampin are currently used in Quebec, and this raises questions about the relevance of using an imported product such as rifapentine.

In order to make an informed decision on whether it should import rifapentine for preventing onset of active TB in people with LTBI who are at risk of developing active TB in Quebec, the ministère de la Santé et des Services sociaux (MSSS) tasked the Institut national d'excellence en santé et services sociaux (INESSS) with producing a state of knowledge report on the use of rifapentine to treat LTBI in populations at risk of developing active TB.

Methodology

In accordance with the INESSS's standards, a systematic review with meta-analyses was performed in order to expand knowledge of the efficacy, adherence and safety of a treatment regimen combining rifapentine and isoniazid, administered once weekly for 3 months (3HP), versus other regimens recommended for LTBI. Other topics reviewed included barriers to LTBI treatment adherence and compliance strategies, guidelines and recommendations for good clinical practices in LTBI management, and registered clinical studies underway. A cost estimate for 3HP, compared to costs for the usual treatment regimens available in Quebec, was also carried out.

Three databases – MEDLINE (Ovid), Embase (Ovid) and Evidence-Based Medical Reviews or EBMR (Ovid) – were used for scientific literature searches in French and English, extending from the database creation date to November 2018, with current awareness done until August 2019. The bibliography of each article selected was also consulted, to identify other relevant papers. Meta-analyses were conducted using aggregate data, based on a randomized logistic regression model that would reflect variability within each study and between studies. All results were summarized by theme. Statements of evidence were assessed by outcome and when possible by study population.

Results

Analysis of scientific data revealed no statistically significant difference between 3HP and the other treatment regimens recommended in Quebec and Canada for preventing active TB in LTBI cases. These analyses revealed that people taking 3HP under directly observed therapy (DOT) completed their treatment 30% more often than did those taking isoniazid as monotherapy once daily for 9 months (9INH) under self-administered therapy (SAT). The difference in adherence between the two treatment regimens – 3HP under DOT and rifampin as monotherapy once daily for 4 months (4RIF) under SAT – is not statistically significant, however. The results reveal that 3HP induces a hepatotoxicity-related reaction in 70% fewer subjects than did 9INH, while the difference in a comparison to 4RIF was not statistically significant. The number of mild or moderate adverse events – while not statistically significant – also tended to be higher after 3HP was initiated, versus 9INH or 4RIF, due to a more pronounced hypersensitivity. Results also demonstrate that, while these events are rare, 3HP recipients had a higher reported systemic drug reactions count than did 9INH recipients. Severe stage 3 and 4 adverse effects, and hospitalisation due to adverse effects, were rare and not statistically significant, but the incidence was greater with 3HP than with 9INH. Finally, the results appear to show a higher treatment discontinuation rate due to adverse effects among patients given 3HP versus 9INH or 4RIF. This difference, however, is not statistically significant.

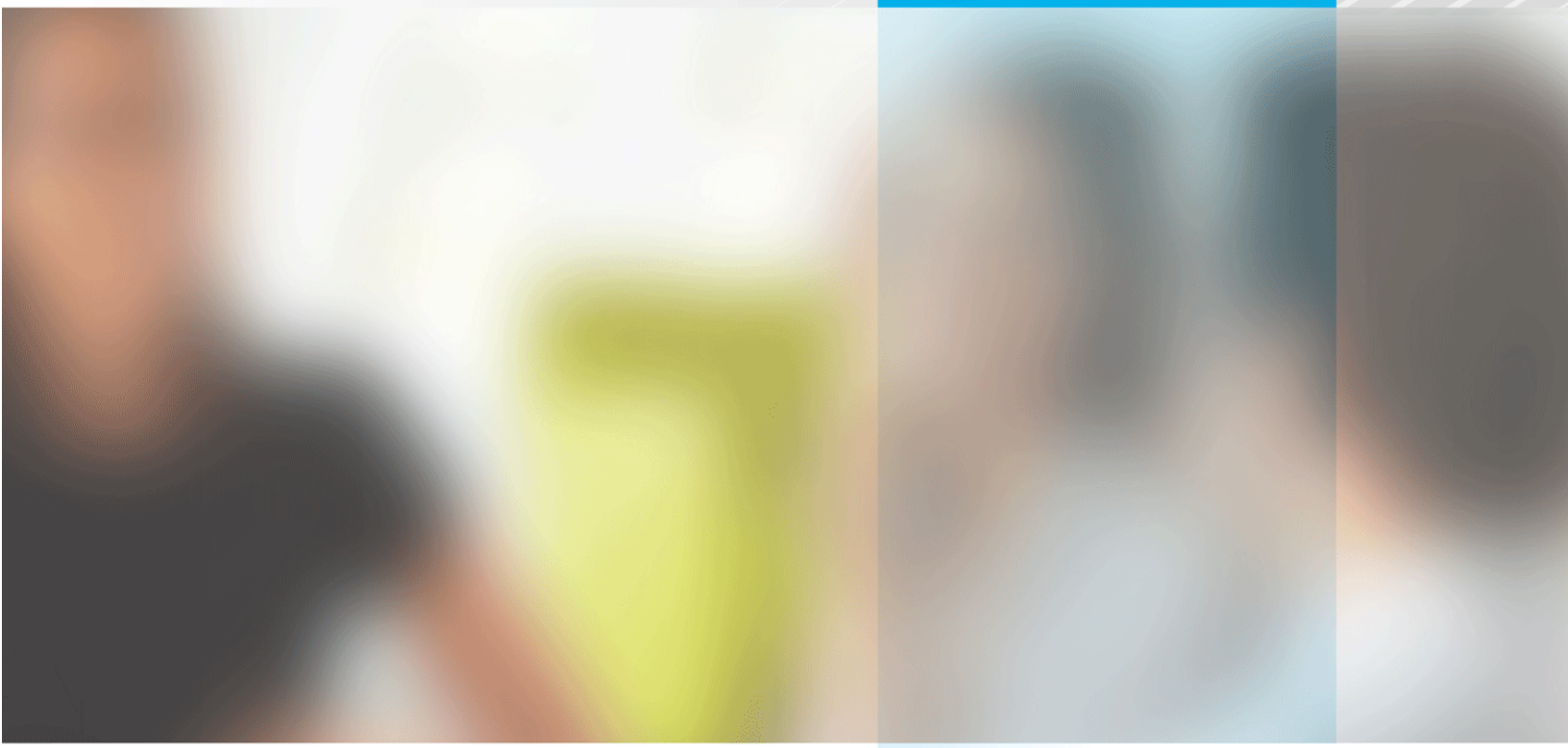
The systematic review for good clinical practices in LTBI treatment, carried out by INESSS, revealed that most organisations recommend administering 3HP to adults and children more than two years of age, to treat LTBI. Some clinical practice guidelines (CPG) suggest that 3HP can be self-administered going forward, whereas the previous recommendation was solely for DOT. Based on the current state of scientific knowledge, the key barriers to treatment adherence are found in marginalised and homeless populations, the main reason being treatment duration. In most situations studied, short treatment periods and administration under DOT help ensure better adherence to LTBI treatment. Social interventions, education, along with culturally sensitive case management, also appear to have a positive impact on LTBI treatment completion rates.

Budget impact analyses were carried out solely at the institutional level, where only the drug cost was taken into consideration. These analyses revealed that, because of its higher cost, the budget impact of 3HP is greater than that of 4RIF, but lower than that of 9INH, for the three Quebec population groups analyzed: the Inuit in Nunavik, prison inmates and the persons in a situation of marginalisation in urban settings.

Conclusions

The results set out in this state of knowledge confirm that 3HP administered under DOT is more beneficial than 9INH under TAA, especially with regard to treatment adherence and hepatotoxicity risk. Additionally, the work done by INESSS adds a systematic review, with new adherence and safety profile comparisons for 3HP and 4RIF, to the body of scientific literature. The lack of a significant variance between these groups is hardly conclusive, however, and new methodologically sound studies directly comparing 3HP

and 4RIF would be needed, in order to ensure these results are more reliable. Given the current state of scientific knowledge, 3HP could represent a new option for preventing the onset of active TB when used to treat LTBI in at-risk populations such as the Inuit of Nunavik, prison inmates and the persons in a situation of marginalisation in urban settings. Pending the completion of new methodologically sound studies that will disprove or confirm a greater risk of severe adverse effects with 3HP than with other treatment regimens, however, benefits and risks based on target population characteristics should factor into the decision to use – or not use – 3HP. In conclusion, the work done thus far should inform any decision made by the MSSS and healthcare settings about importing or not importing rifapentine for combination therapy, with isoniazid, to treat LTBI.



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