Threats to the Effectiveness of Malaria Treatment

J-F Pays

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Abstract In reaction to the speed and ease with which a high level of resistance against *P. falciparum* was induced in vivo in a mouse NOD/SCID IL-Ry^{-/-} model by sub-therapeutic doses of artesunate [2], this text begins a plea for concrete measures to limit the risk of eventually appearing the same phenomenon in the field, including a strengthening of the fight against the use of artesunate oral monotherapy, tablet often under-dosed or artemisinin herbal tea and the adoption of more reliable and more efficient means than those currently used to detect the emergence of resistance earlier and a relaunch of the search for new antimalarials.

Keywords malaria · artesunate · artemisinin · quinine · resistance · antimalarials · NOD/SCID IL-Ry^{-/-} mice · public health

An estimated 3 billion people are at risk of malaria and 200 million are sick each year. Artemisinin, combined with unprecedented global control measures, has reduced mortality by half in recent years, with about 500,000 annual deaths. Artesunate and its derivatives are today the basis of almost all treatments used in the world. The history of malaria shows that widespread use of the few drugs available has always led to resistance. Recent progress may therefore be transient, especially in the area of lethality.

The appearance of a high level of resistance to artesunate in NOD/SCID IL-Ry^{-/-} mice induced by treatment with sub-therapeutic doses as reported in the article published in BMC (2) represents therefore very bad news, likely to call into question the current control strategies. The fact that this resistance is accompanied by almost the same level of resistance to amodiaquine and especially to quinine, the only alternative treatment for the complicated forms of the disease, gives it a particular resonance by raising the fear of

the arrival of the day we would be practically unarmed in face of malaria and of its complicated life-threatening forms.

It is certainly, in the referenced article, results obtained in an experimental model that do not necessarily foreshadow the evolution of resistance in the field, but it would be unreasonable to just wait and hope that this which may have occurred very quickly and at a very high level in animals, will remain a laboratory curiosity and will not occur one day, more or less near or far in at-risk populations. Artemisinin, advocated by some as an alternative to praziquantel to treat schistosomiasis and other cancers of the lung or breast, is a molecule far too valuable for its use to be strictly regulated and to protect it by all means, even to the extreme, to criminalize irresponsible propaganda encouraging its approximate and off-label use of monotherapy and herbal tea from private crops. The threats to artemisinin, which we had heard yesterday and confirmed today, would justify it. The way in which high level resistance to artesunate has been rapidly induced in NOD/SCID IL-Ry^{-/-} mice is in fact comparable to monotherapy, to the taking of an herbal tea whose content of active ingredient is completely unverifiable or the use of under-dosed counterfeit tablets. Despite warnings and bans by WHO to market artemisinin for oral use, dozens or even hundreds of websites still offer artesunate tablets on the internet and many more or less confidential associations continue to promote herbal teas and plant cultivation for personal curative or preventive use, if only to oppose the “international lobby of pharmaceutical companies”

In view of the results to which we refer [1], the usual recommendations of “increasing surveillance” or “closely monitoring the appearance of resistance” now appear to be insufficient. Concrete measures adapted to new data should be taken, such as the adoption of ways to detect resistance earlier and more reliably (e.g. ring-stage survival test (RSA) or in vivo model of NOD/SCID IL-Ry^{-/-} mice despite the difficulties of their implementation and their cost), as well as the revival and support for research today towards neglected new drugs and a vaccine really effective and inexpensive. Failure to do so would, in practice, be resigned to the possibility of a gradual disappearance of the effectiveness of the treatment of the most lethal of all parasitic diseases and its consequences.

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