Review

Antimycobacterial activities of riminophenazines

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Riminophenazines were specifically developed as drugs active against *Mycobacterium tuberculosis* but extensive research over several decades has shown that these compounds are also active against many other mycobacterial infections, particularly those caused by *Mycobacterium leprae* and the *Mycobacterium avium* complex (MAC). Clofazimine, the lead compound in this series, is included in the regimens that are approved by the WHO for the treatment of leprosy and has contributed significantly to the control of that disease, particularly that caused by dapsone-resistant bacteria. Despite early problems, clofazimine has shown clinical efficacy in tuberculosis, in particular that caused by multiple drug resistant strains. Clofazimine does not induce resistance and also inhibits emergence of resistance to isoniazid in *M. tuberculosis*. The efficacy of clofazimine against MAC is more varied and the availability of better drugs has limited its use. Newer riminophenazines, such as B746 and B4157, not only showed increased anti-mycobacterial activity but also produced less skin pigmentation, which is the main drawback of this group of compounds. The most important virtues of riminophenazines, such as intracellular accumulation in mononuclear phagocytic cells, anti-inflammatory activity, a low incidence of drug resistance and slow metabolic elimination, make them attractive candidates for the treatment of mycobacterial infections. It is essential, however, to investigate the newer analogues clinically, while continuing the pursuit of alternate candidates that demonstrate higher anti-mycobacterial activity and lower rates of skin pigmentation.

Introduction

“We ought to look for some agent which is reasonably insoluble, so that it may be phagocytosed by the monocytes and there bring to bear its killing effect on the tubercle bacillus. We want something which will be perhaps phagocytosed by these cells, will remain there for some time, releasing an amount sufficient either to kill or prevent the tubercle bacillus growing and which will not be rapidly excreted.” A. Q. Wells.\(^1\)

The word riminophenazine was coined to denote a group of active phenazine compounds wherein a substituent (R) has been included in the ‘imino’ part of the molecule. Historically, this group of compounds was derived from lichens. At a time when desperate searches were made for compounds active against tuberculosis, lichens constituted an important source, from which several active compounds, e.g. usnic acid and roccellic acid, were derived. One such compound was diploicin, obtained from the lichen *Buellia canescens*.\(^2,3\) Several derivatives of this compound led Barry and associates to the discovery of anilinoaposafranine, which was highly active against tubercle bacilli.\(^4,5\) Encouraged by this finding, Barry’s group\(^5,6\) prepared several structural modifications (R-substitution) mainly at the (NH) imino group; hence the name ‘rimino’ compounds. Among the compounds thus prepared, one, 2-chloro-anilino-5-p-chlorophenyl-3,5-dihydro-3-isopropyl iminophenazine, which was initially called B663 and, later, Lamprene or clofazimine, proved to be highly active (Figure 1). As is discussed below, this compound and its several analogues accumulate preferentially inside the cells of the mononuclear phagocyte system (MPS), previously called the reticuloendothelial system (RES). More interestingly, as is also discussed below, these

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compounds have long half-lives. For these reasons, Barry was tempted to call this compound a ‘tailor made or custom made’ drug, based on the general requisites of an ideal antituberculosis drug, as stated by A. Q. Wells. Participants of the 1957 International Tuberculosis Conference in New Delhi, witnessed the great excitement which Dr. Barry displayed in the announcement of this discovery of a very powerful drug to cure tuberculosis once and for all. This excitement was rather short lived. Although many could confirm the high in-vitro antituberculosis activity of clofazimine, animal studies in the guinea pig model, the then standard animal model for tuberculosis, did not show any activity of clofazimine against experimental tuberculosis. Soon after, Schmidt et al. presented another negative finding of the lack of in-vivo activity in experimental simian tuberculosis. In those days, the standard opinion that prevailed was that to be useful in clinical tuberculosis any compound should demonstrate high activity in the monkey model. These two negative findings rapidly and rather strongly curbed the enthusiasm, and the drug was put to one side for several years. Subsequent studies, however, showed that the reason for the failure of the drug in the guinea pig and monkey models was the poor absorption of the drug by the oral route. It was also shown that, in hamsters and mice, where the drug is well absorbed by the oral route, there was considerable in-vivo activity. The ‘damage’ done to the drug by the early negative findings, however, persisted for a considerable length of time, until its potential in the treatment of leprosy was shown by Browne and Hogerzeh, who adopted the premise that an intracellular drug (clofazimine accumulates inside macrophages to a remarkable degree; see below) should be used for the treatment of an ‘intracellular disease’, leprosy. This finding may appropriately be called the turning point in the chemotherapeutic role of clofazimine: clofazimine is now an important constituent of all the regimens used for the treatment of all types of leprosy.

Following the recognition of the necessity to discover new drugs active against Mycobacterium avium complex (MAC), even before the recognition of involvement of MAC as opportunistic pathogens in patients with AIDS, some studies showed the in-vitro activity of clofazimine against these organisms. A huge amount of literature has since accumulated on the role of clofazimine and its analogues for the treatment of MAC. A few attempts have also been made to explain the usefulness of clofazimine against Mycobacterium marinum and Mycobacterium ulcerans infections. It may be recalled that Runyon grouped these three organisms—Mycobacterium leprae, M. ulcerans and M. marinum—as ‘cooler body pathogens’. Interestingly, because of its unique pharmacology, clofazimine has been investigated for its anticancer activity also. Parallel to these studies, an enormous number of clofazimine analogues have been prepared and tested, with the hope of achieving higher blood concentrations (clofazimine produces very low blood concentrations but high tissue concentrations) and to reduce the bluish-purple skin pigmentation, more conspicuous in fair-skinned individuals, that is a common side effect of the drug. The pigmentation wanes after the drug is withdrawn or when the blood concentrations are low.

In this review, we confine the discussion on the role of clofazimine and its analogues to the treatment of leprosy, tuberculosis and MAC disease. We also provide a brief summary of the interesting pharmacological and immunobiological properties of this group of compounds and their potential implications in targeted drug delivery. Even though there is a considerable literature on the anticancer activity of these compounds we will not discuss this further.

**Chemistry**

Clofazimine (Figure 1) (C_{27}H_{22}C_{12}N_{4}, mol. wt. 473.14, melting point 210–212°C) is deep red to orange under normal conditions. It is a very hydrophobic and will not dissolve in

![Figure 1. Structure of Riminophenazines](image-url)
Antimycobacterial activities of riminophenazines

nonacidic aqueous solutions. It is a basic drug, and exists in a charged form at physiological pH. In alkaline environments and in organic solvents, clofazimine is uncharged and has an intense orange–yellow colouration. As the pH drops, the colour becomes more red and the aqueous solubility increases. In strongly acidic solution, its colour becomes violet. Although the natural cellular pH is insufficiently low to change its colour, the drug is seen in different colours in vivo, perhaps as a result of the ability of the body to reduce it to various extents. Clofazimine can also crystallize inside cells, although this phenomenon does not occur with several other riminophenazines that have different substituents.

As clofazimine does not result in appreciable serum concentrations, and concentrates predominantly in adipose tissues, several analogues have been prepared and tested, mainly with the two objectives of achieving higher serum concentrations and producing less pigmentation. To date, several hundred analogues have been prepared, using substitutions of the R1, R2 and R3 regions (the structures of a representative group of the most promising analogues are given in Figure 1). Comounds with an R1 substitution with chlorine or methoxy or ethoxy groups have increased antibacterial activity and an increased capacity to release superoxide (O$_2^-$) and arachidonate from neutrophils (this aspect is discussed below).

Substitution with chlorine in the two R2 positions results in compounds such as clofazimine. In general, such compounds have higher antituberculosis activity, but also suffer from associated disadvantages of elevation of lipophilicity, fat retention and in many gastrointestinal side effects. Substitutions at the R3 position are designed to further increase the activity. It has been shown that an imino group is essential for the activity. Some compounds in this series are poorly absorbed but have reduced fat solubility and do not crystallize in the body. Among the analogues studied for antimycobacterial activity, few have shown higher activity than clofazimine in the in-vivo models.

Mechanism of action

The biochemical mechanism of action of riminophenazines has not been clearly determined. It has been suggested that generation of intracellular hydrogen peroxide may contribute to the antimycobacterial activity. It has also been advanced that clofazimine inhibits multiplication of organisms by binding to the guanine bases of DNA. Recent studies by Anderson and coworkers have shown that riminophenazines stimulate phospholipase A$_2$ (PLA$_2$) activity leading to accumulation of lysophospholipids, which in turn cause inhibition of Gram-positive bacteria.

Antileprosy activities of riminocompounds

In view of the intracellular accumulation of these compounds in macrophages, it was obvious to study their activity against M. leprae. B663 showed anti-M. leprae activity both in mice and humans. These early encouraging studies led to further human trials and clofazimine proved to be useful in lepromatous leprosy patients, resulting in clinical and bacteriological improvement. Since the first human trial against leprosy, the drug has been in use in endemic areas, especially for the treatment of dapsone-resistant cases. In lepromatous leprosy, treatment with clofazimine not only reduced bacillary burden but also caused reduced complications. Its value in reduction of erythema nodosum leprosum (ENL) has been recognized by many studies. On the basis of the data obtained from several studies, WHO recommended clofazimine for treatment of leprosy and later, recognizing the emergence of dapsone resistance and the efficacy of clofazimine in such cases, WHO has recommended multidrug regimens consisting of dapsone, rifampicin and clofazimine.

A large number of analogues have been synthesized to develop a compound with reduced capacity to cause pigmentation and with improved anti-mycobacterial activity. Structure–activity relationships of some of these compounds have been investigated both in vitro and in vivo against M. leprae. Several analogues have been identified that showed increased in-vitro activity as compared with B663. In-vitro activity was found to increase with chlorination at the R1 and R2 positions and substitution of 2,2,6,6-tetramethylpiperidine (TMP) at the imino nitrogen. In the in-vivo studies, a marked correlation with in-vitro studies was observed, with the TMP derivatives being less effective than B663. The analogues B4087 and B4101 showed slightly better activity than B663 in vivo, and both the analogues caused more pigmentation, whereas analogues B746 and B4100, which produced less pigmentation, showed slightly lower activity in vivo than B663. Even though the investigators observed a positive correlation between pigmentation and in-vivo activity, they also encountered compounds that caused pigmentation without anti-mycobacterial activity. Thus a correlation between pigmentation and anti-mycobacterial activity cannot be made.

Antituberculosis activity

The MICs of B663 for Mycobacterium tuberculosis strains ranged from 1.3 to 3.3 mg/L in Proskauer and Beck medium. The in-vivo activity of B663 was investigated in various experimental animals including mice, guinea pigs, rabbits, hamsters and monkeys. The infected animals were given the drug in the diet and the efficacy was assessed based on the survival times and gross pathology of the internal organs. High activity of B663 against experimental tuberculosis was seen in mice, and good activity in hamsters and rabbits. However, the drug was less effective in guinea pigs and not active in monkeys. These differences in the activity of the drug in different experimental animals have since been attributed to differences in absorption of the
As mentioned above, diet also influences the absorption of the drug and, consequently, the attained tissue concentrations vary. In addition, differences in the pathogenesis of tuberculosis with relative differences in distribution of organisms (intracellular versus extracellular) in different animals could also contribute to the variability in the activity of the drug, as the drug may fail to act on extracellular organisms as the plasma concentrations are always low. Differences in binding to plasma proteins may also be a contributory factor.

One of the cardinal features of clofazimine is the very low frequency of development of resistance to the drug among M. tuberculosis strains, as compared with other antituberculosis drugs. Moreover, at sub-inhibitory concentrations, B663 prevented the development of isoniazid (INH) resistance among M. tuberculosis strains.6

With the introduction of rifampicin and later pyrazinamide for the treatment of tuberculosis, interest in riminophenazines abated, mainly because the drug is not as powerful as either rifampicin or INH. With emergence of multidrug-resistant (MDR) tuberculosis, the interest in riminophenazines was renewed. We have investigated the in-vitro, intracellular and in-vivo activity of clofazimine and several new analogues against susceptible and resistant isolates of M. tuberculosis.44,45 Of the several analogues screened, only five (B746, B4100, B4101, B4154 and B4157) showed in-vitro activity superior to that of clofazimine (Table I). B4100 was found to be toxic to macrophages and, as the intracellular activity of B4101 was similar to that of clofazimine, it was not investigated in vivo. In the experimental chemotherapy studies using M. tuberculosis H37Rv challenge of C57BL/6 mice, two analogues, B746 and B4157 showed equivalent or slightly better activity than clofazimine. Interestingly both compounds showed much less pigmentation of the internal organs and fatty tissue. All the MDR strains tested were found susceptible to clofazimine, B4154 and B4157 with significantly low MICs.44,45 Less pigmentation was observed in the animals treated with B746, B4154 and B4157. Analogues B4157 and B746 need further investigation, especially in combination with other antituberculosis drugs. As single drugs, the chemotherapeutic activities of clofazimine, B746 and B4157 were comparable with those of INH and rifampicin against the H37Rv strain in the animal models we studied.40,41

**Activity against M. avium complex**

Riminophenazines are also being used for the treatment of MAC infections in AIDS patients, even though the first study of the activity of clofazimine against three isolates of MAC was disappointing, with MICs of 5.0–10.0 mg/L. However, in our study,6 with 50 isolates in LJ, 7H10, 7H11 and Sauton’s media we found MICs of 0.4–1.6 mg/L. The MICs were higher in LJ medium (3.2–6.4 mg/L). Further investigations by us42 confirmed the in-vitro activity of clofazimine against MAC and also established the dynamic aspects of its antimycobacterial activity and post-antibiotic effect against MAC in several in-vitro models.55 Lindholm-Levy and Heifets45 compared the in-vitro activities of several riminocompounds at different pHs by the BACTEC method. Of the 12 compounds investigated by them, only B746 showed comparable activity to clofazimine and acidic pH increased the MICs of all the compounds. However, such MICs are significantly lower than the concentrations achievable in macrophages. We investigated the in-vitro activity of eight riminocompounds (two of which were also investigated by Lindholm-Levy and Heifets45) and found that the activity of compound B4100 was two to four times more than that of clofazimine. Two other compounds (B746 and B4101) showed slightly lower activity than clofazimine (V. M. Reddy and P. R. J. Gangadharam, unpublished data). Despite increased in-vitro activity, B4100 was slightly toxic to macrophages. We extended these studies in vivo using the beige mouse model and found that clofazimine was fairly active against MAC. In one study we compared the in-vivo activity of B746 with that of clofazimine46 and, in another, we compared the in-vivo activity of B4100 and B4101 with that of clofazimine. In both studies clofazimine was superior to the rest of the compounds given alone or in combination with other drugs (V. M. Reddy and P. R. J. Gangadharam, unpublished data).

Several in-vitro and macrophage studies have demonstrated consistent activity of clofazimine against MAC strains.44,45 In macrophages clofazimine was found to be synergic with clarithromycin44 as well as roxithromycin.46 Yajko et al.,47 while studying the in-vitro and intracellular activities of several combination of drugs, found that clofazimine combinations, although less effective in vitro, showed good activity in macrophages. They found clofazimine with clarithromycin, rifabutin and ethambutol was the most effective combination.

In experimental studies in beige mice, clofazimine and B746 showed excellent activity against MAC. Combination chemotherapy studies in beige mice conducted by us49,50 and others51 have extensively investigated the chemothera-

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**Table I. In-vitro activities of clofazimine analogues against M. tuberculosis isolates**

<table>
<thead>
<tr>
<th>Analogue</th>
<th>MIC range (mg/L)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;&quot; (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clofazimine</td>
<td>&lt;0.06–2.00</td>
<td>≤1.00</td>
</tr>
<tr>
<td>B746</td>
<td>0.06–0.50</td>
<td>0.25</td>
</tr>
<tr>
<td>B4101</td>
<td>0.12–1.00</td>
<td>0.50</td>
</tr>
<tr>
<td>B4100</td>
<td>0.06–0.50</td>
<td>0.25</td>
</tr>
<tr>
<td>B4154</td>
<td>≤0.06–0.50</td>
<td>0.25</td>
</tr>
<tr>
<td>B4157</td>
<td>≤0.06–0.12</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*Six drug-susceptible isolates, seven isolates resistant to a single drug and seven MDR isolates.*
Antimycobacterial activities of riminophenazines

peutic potential of clofazimine against disseminated MAC disease. Ji et al.\textsuperscript{11} attributed the excellent chemotherapeutic activity of clofazimine in combination with other drugs to the carryover of the drug during enumeration of cfu in the organs. However, our studies of the drug concentrations in the organs and possible concentrations that could be attained in agar plates after appropriate dilution and plating showed that carryover does not occur.\textsuperscript{41,52}

There have been several clinical studies involving clofazimine for the treatment of MAC disease. Although few studies were done before the advent of AIDS, more were done on MAC patients with AIDS. \textsuperscript{10,54–58} In the limited studies by Davidson et al.,\textsuperscript{53} dealing with MAC patients without AIDS, clofazimine given alone did prevent disseminated disease, though only slight improvement of sputum conversion was seen. Masur et al.\textsuperscript{59} investigated clofazimine (100 mg daily) with either 150 or 300 mg of rifabutin and a combination of one or more other drugs such as amikacin, isoniazid, streptomycin, ethambutol or rifampicin. With all the drugs, bacteraemia persisted for a long time and sputum negativity occurred in only two of the 13 patients. Young\textsuperscript{19} found that a combination of clofazimine (50–100 mg/day) and amikacin (7.5 mg/kg im or iv every 12 h), with ethambutol (15–25 mg/kg/day) and rifampicin (600 mg/day) would be effective. The massive uncontrolled study assessing the role of rifabutin along with several other drugs, including clofazimine, did not identify any beneficial role for clofazimine.\textsuperscript{60}

More recently, some other clinical studies have failed to determine any beneficial role for clofazimine against MAC. A comparative assessment of clofazimine with ethambutol and rifampicin for the clearance of MAC bacteraemia in AIDS patients showed that only ethambutol was effective. Similarly, a comparative study of a regimen comprising clofazimine (100 mg), rifampicin (600 mg), ethambutol (15 mg/kg) and ciprofloxacin (150 mg/kg) bd and a three drug regimen consisting of rifabutin (600 mg), ethambutol (15 mg/kg) and clarithromycin (1000 mg) bd, showed that the latter was more effective, clearing bacteraemia more frequently and more rapidly. By far the most serious drawback to the clinical usefulness of clofazimine against MAC disease came from a preliminary analysis of a continuing study by the AIDS Co-operative Treatment Group (ACTG) and Community Program for Clinical Research on Aids (CPSRA) which investigated, in an open-label study, the tolerability and efficacy of clarithromycin and ethambutol in combination with or without clofazimine. An interim progress report, kindly provided by Dr Barbara Loughon (personal communication, 1997) showed that ‘clofazimine adds no measurable bacteriological or clinical benefit to clarithromycin and ethambutol, and may result in excessive mortality, although the exact mechanism of this is not apparent. It is therefore unwarranted at this time to add clofazimine to clarithromycin and ethambutol for the initial treatment of disseminated MAC disease.’ On the basis of these data, the Division of AIDS of the NIAID, NIH, USA recommended that investigators contact patients receiving clofazimine therapy in their study and advise them to discontinue clofazimine. This decision has been taken by the Division of AIDS, even though it is realized that clofazimine is in the salvage arm and that the studies are still in progress (and, indeed are close to completion).

The story of clofazimine in treatment of MAC disease, particularly dealing with disseminated MAC disease is confusing. Although the lack of activity can be explained to some extent by the lack of high serum levels, a unique deficiency of this drug, it is difficult to explain the high mortality caused by this drug. Earlier studies\textsuperscript{61} have indicated that prolonged treatment with clofazimine results in higher levels in bone marrow cells, causing severe toxicity. In AIDS patients, with a greater vulnerability of the bone marrow cells, it could be a possible explanation.

Metabolism of clofazimine

Clofazimine is metabolized by humans into three compounds (i) 3-hydroxyanilino-10-(p-chlorophenyl)-2,10-dihydro-2-isopropyliminophenazine (Metabolite 1), (ii) 3-(β-D-glucopyranosiluronic acid)-10-(p-chlorophenyl)-3,10-dihydroxy-2-isopropyliminophenazine, (Metabolite 2) and (iii) 3-(p-chloroanilino)-10-(p-chlorophenyl)-4-(β-D-glucopyranosiluronic acid)-2-isopropyliminophenazine, (Metabolite 3) (Figure 2). Metabolite 1 is believed to be formed by a hydrolytic dehalogenation reaction, metabolite 2 by hydrolytic deamination followed by glucuronidation, and metabolite 3 by hydration followed by glucuronidation. All three metabolites occur at a very low concentration, totalling less than 1% of the drug (0.2%, 0.25% and 0.2% for the three metabolites, respectively). Feng et al.\textsuperscript{62} who are the only researchers who have investigated this aspect thoroughly, stated that these low amounts are probably due to the long retention time of the drug in the body. There is no evidence whether the metabolites have any antimycobacterial activity.

Pharmacology

Interestingly, the extent of absorption of the drug varies in different animals following oral administration. Some of the early results in guinea pigs and monkeys have been attributed to inadequate absorption of the drug. In its powder form it is poorly absorbed in guinea pigs and in man, whereas it is well absorbed in mice, hamsters and rabbits. To enhance its absorption, the drug is presented in micronized form. Administration of the drug with food containing fat and proteins has been reported to increase the bioavailability.\textsuperscript{63} The most important feature of riminocompounds, and especially of B663, is the characteristic accumulation of the compounds in the tissues, particu-
V. M. Reddy et al.

**Figure 2.** Metabolic products.

larly the RES and fatty tissues in general. In addition to skin, the drug accumulates in subcutaneous fat, adrenals, heart, liver, lungs, pancreas, kidneys, spleen, bone marrow and the lamina propria of the jejunum. Despite its accumulation in most organs, the drug seems to cause remarkably few life-threatening toxicities.  

The main adverse effects of clofazimine are skin pigmentation and gastrointestinal disturbances. Abdominal pain, diarrhoea, nausea, vomiting and gastrointestinal intolerance are the main complaints. The drug is mainly excreted in urine, sputum, sweat and breast milk. Because of its concentration in tissues and its slow excretion, the drug has a long half-life of about 70 days. In general, the drug produces low plasma concentrations as compared with high tissue concentrations. The internal organs and the skin turn an orange colour upon prolonged treatment. Crystalline deposits of the drug have been demonstrated in the phagocytic cells. In its micronized or powder form, mice given 25 mg/kg in their diet for 28 days produced drug concentrations of 800, 4000 and 800 mg/g in lungs, spleen and fat tissue respectively, and the plasma concentrations were 3.0 mg/L. Increased dosage or extended period of treatment does not affect the plasma concentration. In guinea pigs the plasma concentrations of the drug never reached the concentrations observed in mice or rats. The concentrations in the lungs were, in general, high. In humans given a 600 mg/kg dose orally, the serum concentrations were 3–4 mg/L. As the drug accumulates in the organs, cessation of treatment results in slow release of the drug from the tissue deposits and its recirculation.

**Other pharmacological activities of riminophenazines**

Riminophenazines, in addition to their antimycobacterial activity, also exhibit pro-oxidative activity. The compounds per se stimulate superoxide anion production only to a slight extent but they prime the neutrophils and mononuclear cells to enhance release of reactive oxygen radicals following stimulation with different stimuli such as n-formyl-met-leu-phe (FMLP), phorbol myristate acetate (PMA), arachidonic acid, calcium ionophore and opsonized zymosan. The pro-oxidative activity is mediated through stimulation of phospholipase A₂ (PLA₂) resulting in increased accumulation of intracellular lysophosphatidylcholine and arachidonic acid in the phagocytic cells, which, in turn, causes release of superoxide. The pro-oxidative effect of riminophenazines depends on the structure of the compounds, particularly the presence of an alkylimino group at position 2 and halogenation. Of the several analogues investigated for the pro-oxidative activity, compound B669 possessed maximum activity. Clofazimine and B669 have been shown to reverse the inhibitory effect of *M. tuberculosis*-derived 25 kDa protein on phagocytic functions.

Apart from antimycobacterial activity, the other pharmacological activity of clofazimine of significant importance is its anti-inflammatory effect. Anti-inflammatory activity is of great value in management of cases of lepromatous leprosy with ENL. Clofazimine has also been used successfully for the treatment of other inflammatory diseases such as pyoderma gangrenosum, systemic lupus erythematosus, and vitiligo. The immunosuppressive and anti-inflammatory activity of clofazimine has been
attributed to stimulation of prostaglandin-E₂ from macrophages. ¹¹ ¹³

Another interesting immunopharmacological property of clofazimine offers some innovative opportunities. As discussed above, one of the properties of clofazimine is its rapid localization within phagocytes. In this capacity, it is similar to liposomes. Recent advances in the chemistry of clofazimine and its analogues plus available knowledge on the structure–activity relationships allowed the specific parts of the compound that can be used to tag on to other compounds and transport them into macrophages as a ‘Trojan Horse’ to be identified. For instance, substitution at R₂ (see the discussion above) with a carboxy group (—COOH) or with an N-protected amino acid group, results in compounds with increased transportation capacities. In fact, indomethacin has already been successfully tagged on to a riminophenazine, B₃₆₄₀, and transported into phagocytes more efficiently (J. F. Sullivan, unpublished observations). This property of riminophenazines would provide an innovative method to transport drugs into cells.

Conclusion

As Dr. Barry emphasized, riminophenazines, particularly clofazimine, are innovative custom-made drugs, developed in a logical sequence. If the goal of new drugs for treatment of mycobacterial diseases is primarily to kill intracellular organisms, these are ideal candidates. It has been so for the treatment of leprosy, which is primarily an intracellular disease. With tuberculosis, clofazimine has almost been forsaken owing to the use of inappropriate animal models in the early studies and the availability of other effective bactericidal drugs. The very fact that, so far, no clofazimine-resistant tubercle bacilli have been reported might suggest it to be a suitable drug for the treatment of tuberculosis, particularly MDR tuberculosis. Of course, further studies are needed to determine the timing (early phase or maintenance phase, as with pyrazinamide) and dose, etc. Development of more promising analogues such as B₄₁₅₇ in a logical sequence. If the goal of new drugs for treatment of mycobacterial diseases is primarily to kill intracellular organisms, these are ideal candidates. It has been so for the treatment of tuberculosis, clofazimine has almost been forsaken owing to the use of inappropriate animal models in the early studies and the availability of other effective bactericidal drugs. The very fact that, so far, no clofazimine-resistant tubercle bacilli have been reported might suggest it to be a suitable drug for the treatment of tuberculosis, particularly MDR tuberculosis. Of course, further studies are needed to determine the timing (early phase or maintenance phase, as with pyrazinamide) and dose, etc. Development of more promising analogues such as B₄₁₅₇

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